DUKE-ELDER LECTURE

SYSTEMIC ARTERIAL BLOOD PRESSURE AND THE EYE

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In modern society, particularly in the industrialised world, the leading cause of death during the past half-century has been cardiovascular disease. Alterations in systemic blood pressure (BP), especially hypertension, have been recognised as one of the most important risk factors. In the middle-aged and elderly population there is a trend towards a rise in BP which often becomes steeper with advancing age.[2] Systemic mortality and morbidity are markedly higher in hypertensives than in normotensives; for example, hypertensives are 7 times as likely to develop stroke as normotensives, 4 times as likely to have congestive heart failure, 3 times as likely to have coronary artery disease, and twice as likely to have peripheral arterial disease; and the hypertensive's risk of total and cardiovascular mortality is twice that of the normotensive.[3] Similarly, it is well established in the literature that hypertension plays an important role in the pathogenesis of a variety of ophthalmic conditions producing severe visual impairment.[4–9] Recently emerging evidence indicates that arterial hypotension also plays an important role in the development of several systemic and visually crippling conditions.[9,10] All these considerations make alteration in BP an important topic for ophthalmologists.

For over a decade I have investigated experimentally[11–25] and clinically[7,8,10,26,27] the effects of arterial hypertension and also arterial hypotension on the eye, and their role in the development of various ocular and optic nerve head (ONH) vascular disorders. The following account is a very brief review of our findings so far.

First, in order to understand fully the mechanism of production of the various fundus lesions seen with arterial hypertension and the role played by alterations in BP in the pathogenesis of various ocular and ONH vascular disorders, it is essential to comprehend some of the basic issues on the subject.

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BACKGROUND

Basic Properties of the Ocular and ONH Vascular Beds

Blood Flow

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

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

Perfusion pressure = Mean BP minus intraocular pressure. Perfusion pressure is also equal to mean arterial pressure minus venous pressure in a vascular bed. Normally the central retinal venous pressure is slightly higher than the intraocular pressure so that, for all practical purposes, intraocular pressure is a good index of the ocular venous pressure.

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

From this formula, it emerges that the ocular and ONH blood flow depends upon (i) resistance to blood flow, (ii) BP and (iii) intraocular pressure. The pathophysiology of the factors controlling the blood flow is discussed in detail elsewhere.[28] Very briefly, the resistance to blood flow, according to Poiseuille's Law, is directly proportional to blood viscosity and the length of the vessel, and is inversely proportional to the fourth power of the radius of the vessel. Therefore, the resistance depends upon the state and calibre of the ocular arteries, which are in turn influenced by hypertensive arterial changes and efficiency of autoregulation of blood flow.

Blood Flow Autoregulation

The goal of autoregulation is to maintain a relatively constant blood flow in a tissue during changes in perfusion pressure (Fig. 1). This is an important blood flow regulating mechanism. The retinal and ONH vascular beds have autoregulation, while the choroidal vascular bed does not.[24] The exact mechanism and site of autoregulation are still unclear, except that autoregulation most probably operates by altering the vascular resistance. Generally it is considered a feature of the terminal arterioles; so with the rise or fall of BP beyond normal levels, the terminal arterioles constrict or dilate, respectively, to regulate the vascular resistance and thereby the blood flow. Recent studies suggest that vascular-endothelial-derived vasoactive agents (e.g. the vasoconstrictors endothelin-1, thromboxane A_2 and prostaglandin H_2, and the vasodilator nitric oxide) profoundly modulate local vascular tone[29] and, thereby, may play a role in autoregulation.[9]

Factors Causing Breakdown of Autoregulation

Autoregulation may be disrupted by alterations in BP via a variety of local and systemic causes, including the following:

1. *Rise or fall of perfusion pressure beyond the critical autoregulatory range.* Autoregulation operates only over a critical range of perfusion pressure; with a rise or fall of perfusion pressure beyond the critical range, autoregulation becomes ineffective and breaks down (Fig. 1). Thus autoregulation does not protect the tissues all the time. If the perfusion pressure goes above the autoregulation range (as in malignant hypertension) it damages the tissue; and if it falls below the range (as in marked arterial hypotension) that subjects the tissue to a risk of ischaemia.

2. *Arterial hypertension.* In this, the range of autoregulation shifts to higher levels to adapt to high BP[15] (Fig. 1). Although such an adjustment improves the patient's tolerance to high BP, it makes him or her correspondingly less tolerant to low BP, so that a level of hypotension which would normally be quite safe becomes dangerous. Under such circumstances, a large, sudden fall of BP in a hypertensive (spontaneously, as occurs during sleep, or because of over-treatment) can cause the perfusion pressure to fall below the autoregulatory range and result in systemic and/or ocular vascular accidents,[10,15] as discussed later.

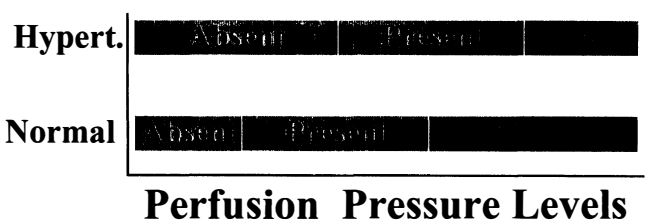


Fig. 1. *A diagrammatic representation of blood flow autoregulation range at different perfusion pressures in normal persons and in hypertensives (Hypert.). 'Absent' and 'present' denote absence or presence of the autoregulation.*

3. *Changes in size of the lumen of the pre-capillary arterioles.* The main factor normally regulating the blood flow is thought to be the size of the lumen of the pre-capillary arterioles. Arteriolar changes in hypertension are well known. These include vasospasm, vasodilation,[14] arteriolosclerosis, drug-induced vasoconstriction or dilatation (by antihypertensive drugs: beta-blockers as vasoconstrictors and calcium-channel blockers as vasodilators) or vasoconstriction caused by angiotensin (leaked into ONH and choroid:[15,16] see below). All these arteriolar changes in hypertension can interfere with autoregulation.

4. *Changes in vascular endothelial function.* These occur early in the course of vascular diseases. In hypertension morphological and functional alterations in endothelial cells occur and basal formation of nitric oxide (a vasodilator) is reduced.[30] Reduced formation of dilating agents by the endothelium may lead to unopposed action of endothelin (a powerful vasoconstrictor), causing vasoconstriction and interfering with autoregulation. Experimental data suggest that endothelial dysfunction develops as BP increases and the dysfunction is related to the level of the BP. Therefore endothelial dysfunction may contribute to hypertensive vascular complications and accidents.[30] There is evidence to suggest that damage to vascular endothelium (associated with abnormalities in production of endothelial vasoactive agents) also occurs in arteriosclerosis, atherosclerosis, hypercholesterolaemia, ageing, diabetes mellitus, ischaemia and for other so far unknown causes;[9,29,30] these conditions are often associated with arterial hypertension and would aggravate the situation.

Blood–Ocular Barrier

The retina has a blood–retinal barrier which is produced by tight cell junctions between the endothelial cells of the retinal vessels and between the retinal pigment epithelial (RPE) cells – the former blocking movement of macromolecules from the lumen of the retinal vessels outwards and the latter preventing leakage of fluid from the choroid into the retina. Malignant arterial hypertension may derange both the blood–retinal barriers. The choroid and ONH, by contrast, do not possess a blood–ocular barrier. In the choroid, numerous large fenestrations in the choriocapillaris allow profuse leakage of plasma proteins and fluid into the choroidal interstitial space. In the ONH the border tissue of Elschnig (separating the peripapillary choroid and

ONH) allows the choroidal interstitial tissue fluid to leak into the ONH from the peripapillary choroid, although the blood vessels in the ONH have a blood–optic nerve barrier because of tight cell junctions.[31]

Autonomic Nerve Supply

It is generally agreed that the vessels in the retina have no autonomic nerve supply, but the choroidal vascular bed is richly supplied by the autonomic nerve supply – both sympathetic and parasympathetic nerves.[24]

Retinal Arterioles

In the retina the so-called retinal arteries are in fact arterioles because they are ≤100 μm in diameter and possess neither an internal elastic lamina nor a continuous muscular coat.[24]

Pathophysiology of Arterial Hypertension

The pathophysiology of arterial hypertension is still not fully understood. Arterial hypertension is considered a multifactorial disease secondary to the interaction of many abnormalities, including the following:[32]

1. *Abnormalities in cell membrane* resulting in defective membrane control over intracellular calcium concentration.
2. *Abnormalities of calcium metabolism* causing rise in cytoplasmic calcium which in turn causes increased tone of the arteriolar smooth muscle.
3. *Abnormalities of sodium metabolism* from inherited difficulty in the kidney's ability to eliminate sodium.
4. *Abnormalities of potassium metabolism* affecting the biosynthesis of aldosterone and renin release.
5. *Abnormalities of central nervous system* including abnormal release of humoral factors (e.g. natriuretic factor, vasopressin), that increase sympathetic discharge and increase neurogenic vasomotor tone.
6. *Abnormalities of prostaglandins.*
7. *Abnormalities of vascular endothelial-derived vasoactive agents*, such as endothelin-1 (a powerful vasoconstrictor) and nitric oxide (a vasodilator).
8. *Genetic effects* on BP, which are polygenic in nature and play an important role in the development of arterial hypertension.
9. *Abnormalities of the renin–angiotensin–aldosterone system,* which available evidence strongly indicates play an important role in the development and maintenance of renovascular malignant arterial hypertension.[13]

SYSTEMIC ARTERIAL HYPERTENSION

Arterial hypertension can produce various visual and fundus abnormalities either by direct effect on the ocular and ONH vessels or indirectly via systemic circulatory disturbances.

Hypertensive Fundus Lesions

Since the first description of hypertensive fundus changes in 1859 by Liebreich,[33] a massive literature, based on both clinical and experimental studies, has accumulated on the subject. Nevertheless, it still remains a centre of controversy. While clinical observations and studies in patients are extremely helpful in understanding a disease process, they have limitations. Over recent years, our ability to produce malignant arterial hypertension experimentally in primates,[13] the advent of fluorescein fundus angiography and its application in hypertensive fundus changes,[14–16,19–23] other modern investigative techniques,[11,12,34–37] and an understanding of anatomical and physiological properties of the ocular and ONH vascular beds (discussed above) have helped markedly to improve our understanding of the subject. The following account of fundus changes in malignant arterial hypertension is essentially based on our experimental studies on the subject in rhesus monkeys,[11–23] supplemented by my clinical experience in patients with malignant arterial hypertension.

In the past, hypertensive fundus changes were described as 'hypertensive retinopathy'; but the retinal, choroidal and ONH blood vessels, because of their different anatomical and physiological properties (discussed above), respond differently to malignant arterial hypertension. Our studies[11–23] on the subject have also revealed that in fact fundus changes in malignant arterial hypertension fall into three distinct and unrelated types of manifestations – (i) hypertensive retinopathy, (ii) hypertensive choroidopathy and (iii) hypertensive optic neuropathy – a fact not fully appreciated in the past, as is evident from the brief description below.

I. Hypertensive Retinopathy

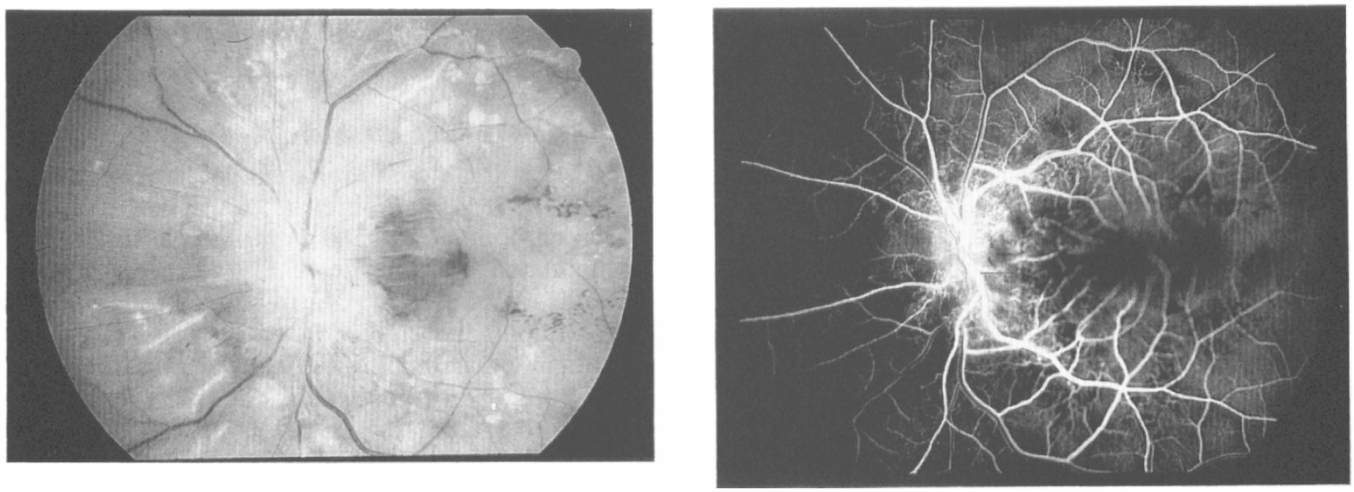
The lesions seen in hypertensive retinopathy comprise the following vascular and extravascular retinal lesions, although in some of the latter the primary factor may be retinal vascular derangement:[18]

Retinal vascular lesions

Retinal arteriolar changes[19]
Focal intraretinal periarteriolar transudates (FIPTs)[14]
Inner retinal ischaemic spots (cotton-wool spots)[20]
Retinal capillary changes[20]
Retinal venous changes[17]
Increased permeability of the retinal vascular bed[14,22]

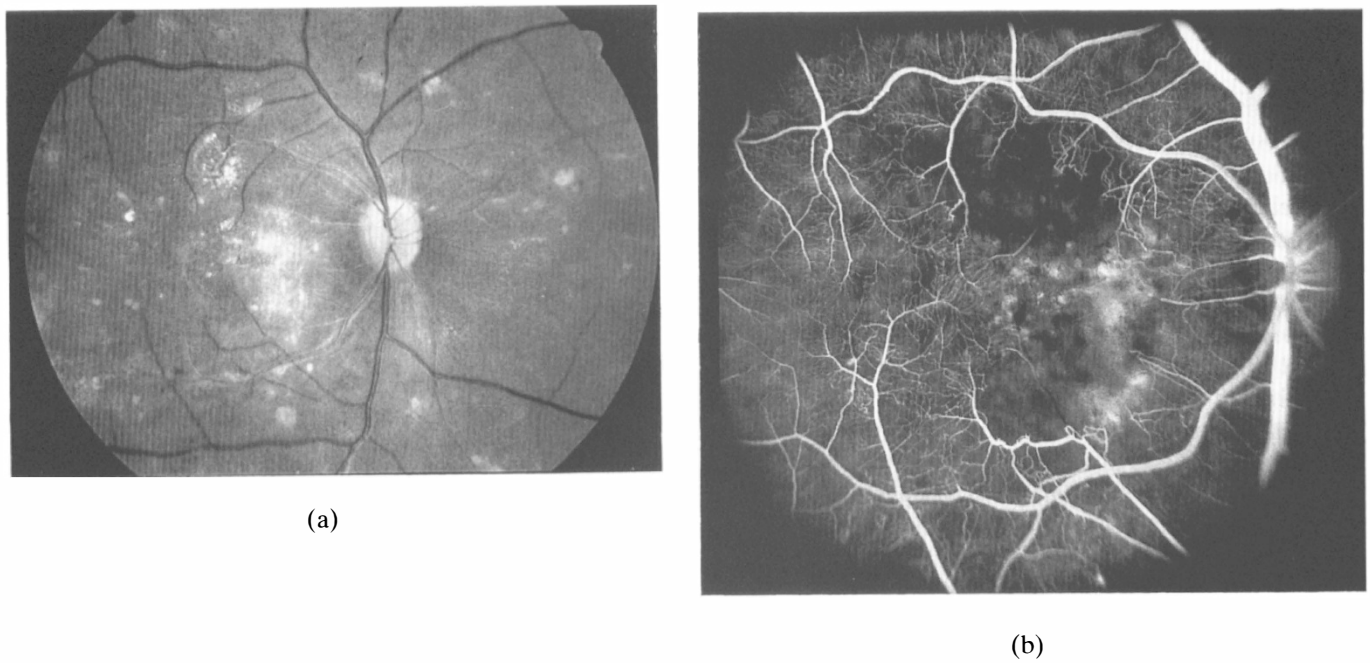
Extravascular retinal lesions

Retinal haemorrhages[17]
Retinal and macular oedema[19,22]



(a) (b)

Fig. 2. *Fundus photograph (a) and fluorescein angiogram (b) of left eye of a hypertensive rhesus monkey with systolic BP 200 mmHg. (a) shows marked attenuation of retinal arterioles, retinal and macular oedema, FIPTs, retinal haemorrhages and extensive macular serous retinal detachment. (b) shows normal calibre of the retinal arterioles (compare with marked narrowing of those seen on ophthalmoscopy in (a). Reproduced from Hayreh* et al.[14] *(a) and Hayreh* et al.[19] *(b).*



(a)

(b)

Fig. 3. *Fundus photograph of right eye of a hypertensive rhesus monkey with systolic BP 204 mmHg. Optic disc shows pallor, sheathing of fine retinal arterioles and other hypertensive fundus changes. Fluorescein angiogram shows normal calibre of the major retinal arterioles (in spite of marked narrowing of retinal arterioles on ophthalmoscopy), occlusion of sheathed arterioles, extensive retinal capillary non-perfusion and some intraretinal microvascular abnormalities. Reproduced from Hayreh* et al.[19]

Retinal lipid deposits ('hard exudates')[21]
Retinal nerve fibre loss[20]

A brief account of these lesions follows.

A. Retinal Vascular Lesions

Retinal Arteriolar Hypertensive Changes

It is best to discuss separately the changes involving the ophthalmoscopically visible main arterioles, and the terminal arterioles, which are usually not readily seen on ophthalmoscopy. In our studies (described in detail elsewhere[14,19,20]) we particularly investigated the arteriolar changes in malignant hypertension.

Narrowing and other changes in the *main retinal arterioles* on ophthalmoscopy have been described as classical manifestations of hypertensive retinopathy associated with malignant hypertension, with arteriolar 'spasm' (localised or generalised) universally reported as typical. We were particularly interested in studying these changes, both during the early,

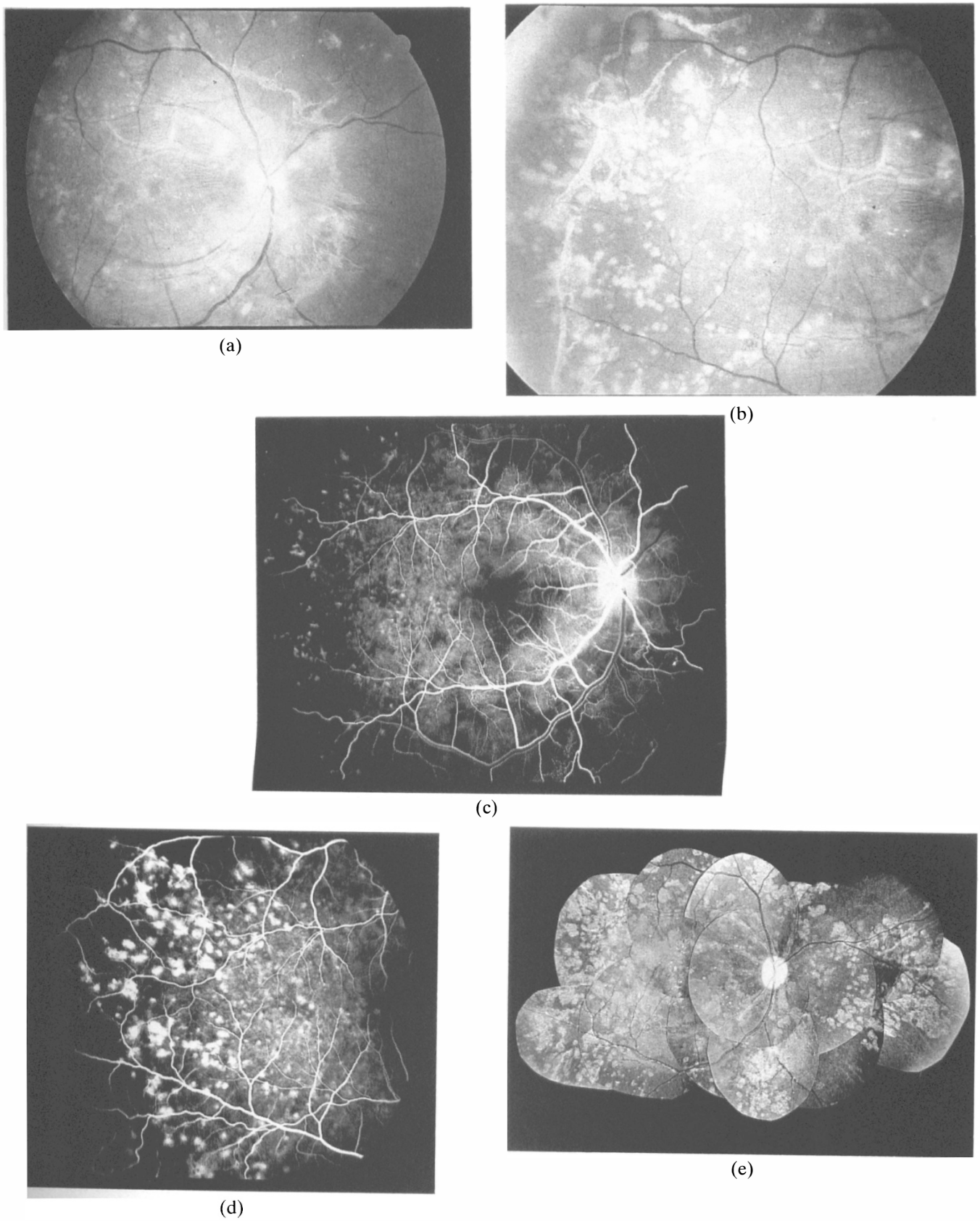
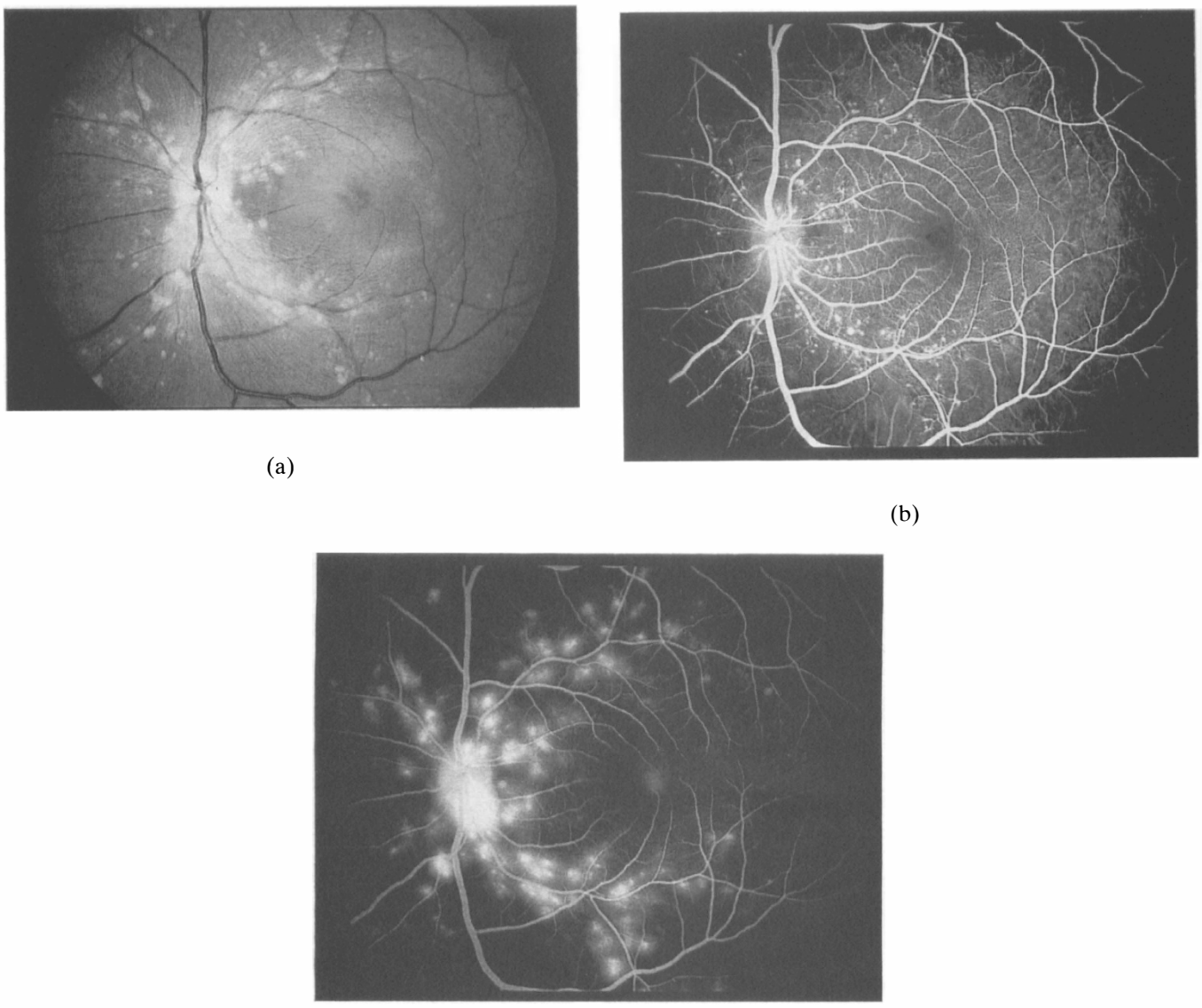


Fig. 4. *Fundus photographs (a, b, e) and fluorescein angiograms (c, d) of right eye of a hypertensive rhesus monkey with systolic BP 190 mmHg (a–d) and 230 mmHg (e). (a, b) Fundus photographs of posterior fundus and temporal periphery, respectively, show extreme attenuation of retinal arterioles, microcystic macular oedema, serous macular retinal detachment, multiple acute focal RPE lesions and hypertensive retinopathy lesions. (c) shows normal calibre of retinal arterioles, in spite of marked narrowing of the arterioles seen on ophthalmoscopy in (a). (c, d) show fluorescein staining of acute focal RPE lesions – early in (c) and late in (d). (e) shows late extensive RPE degenerative lesions, optic atrophy and retinal arteriolosclerosis. Reproduced from Hayreh* et al.[16] *(b, d, e) and Hayreh* et al.[19] *(a, c).*



(a)

(b)

(c)

Fig. 5. *Fundus photograph (a) and fluorescein angiograms (b, c) of left eye of a hypertensive rhesus monkey, with systolic BP 204 mmHg. (a) shows multiple FIPTs (along major retinal arterioles and their main branches). (b, c) show evolution of fluorescein-leaking spots corresponding to the punctate retinal opacities seen in (a). Reproduced from Hayreh* et al.[14]

acute phase of hypertensive retinopathy and later on during the chronic phase.[19]

During the early, acute phase of hypertension, comparison of pre-hypertensive fluorescein fundus angiograms with those during the fully developed hypertensive retinopathy revealed *no* evidence at all of 'spasm' or narrowing in these arterioles, although ophthalmoscopy showed 'pseudo-narrowing' (generalised or localised) – an ophthalmoscopic artefact produced by retinal oedema partially masking the arterioles from the sides (Figs. 2–5, 6a,b); this contradicts the classical teaching on retinal arteriolar 'spasm' or narrowing as the typical feature of malignant hypertension.

After prolonged hypertension, the following changes were observed in the retinal arterioles:

1. Arteriolosclerosis (and associated localised or generalised narrowing and other changes) described as features of hypertensive retinopathy in the literature did develop *but were not early signs* of hypertensive retinopathy (Figs. 4e, 6c, d). Retinal arteriolosclerosis seen in chronic hypertension represents what has been described as 'copper-wire arteries' in the literature because of increased ophthalmoscopic reflex from the wall of the sclerosed retinal arterioles.
2. Increased tortuosity of sclerotic arterioles may also be seen (Fig. 6c, d).
3. Occlusion of a few of the fine arterioles in the distribution of the inner retinal ischaemia spots (cotton-wool spots) may develop (Figs. 3, 6c, d).

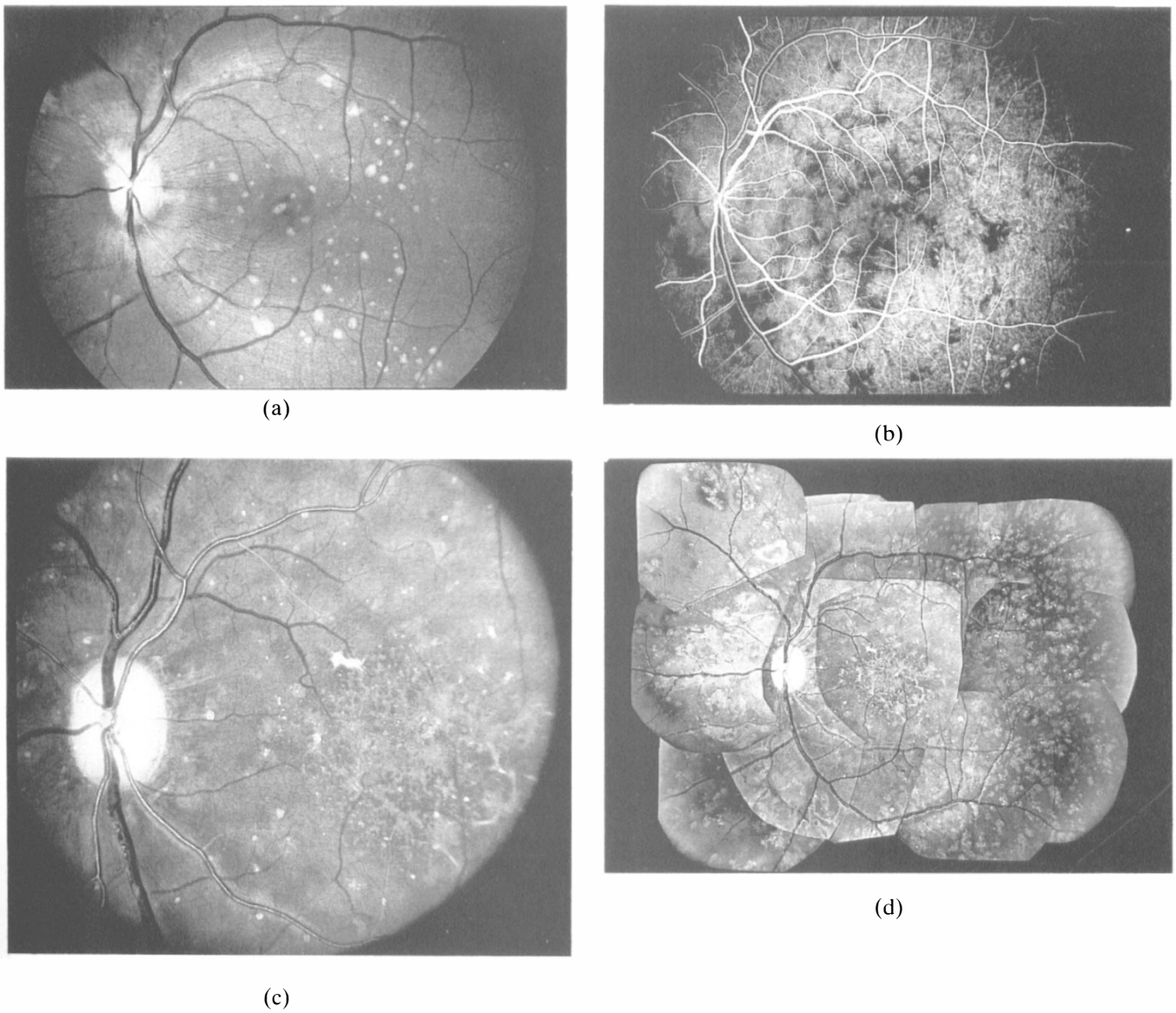


Fig. 6. *Fundus photographs (a, c, d) and fluorescein angiogram (b) of left eye of a hypertensive rhesus monkey with systolic BP 202 mmHg (a, b) and 220 mmHg (c, d). (a) shows multiple white acute focal RPE lesions, in addition to a few FIPTs (along the retinal arterioles). (c, d) show late extensive RPE degeneration, drusen, retinal arteriolosclerosis and optic atrophy. Reproduction from Hayreh* et al. *[16] (a, d) and Hayreh* et al.*[19] (c).*

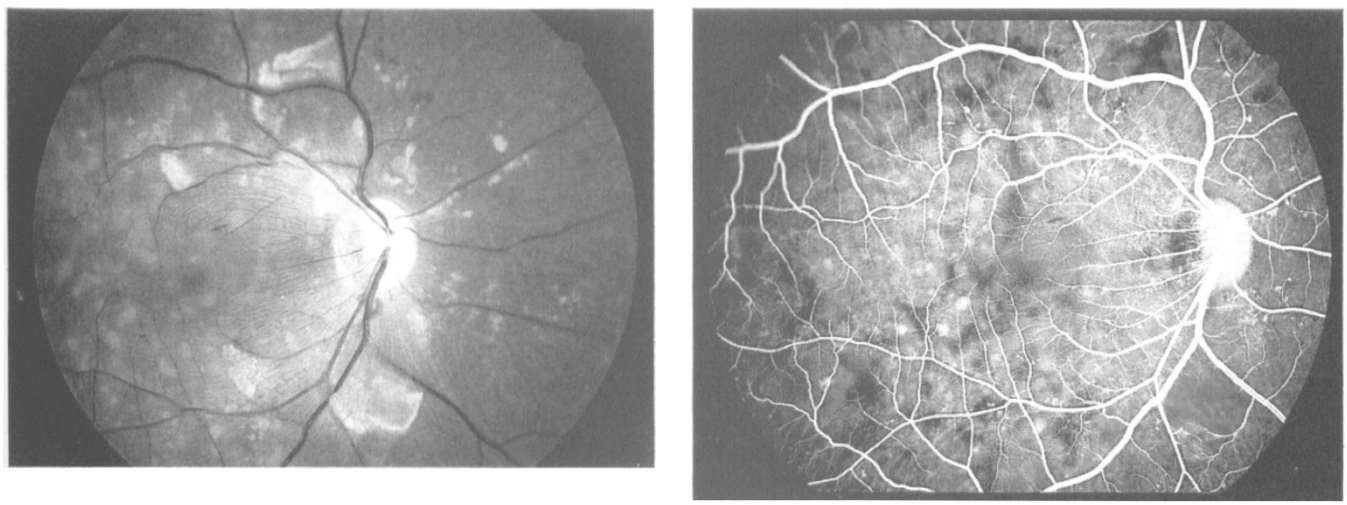


Fig. 7. *Fundus photograph (a) and fluorescein angiogram (b) of right eye of a hypertensive rhesus moneky with systolic BP 238 mmHg, show multiple FIPTs, inner retinal ischaemic spots and focal RPE lesions. (b) also shows areas of retinal capillary non-perfusion in the distribution of inner retinal ischaemic spots. Reproduced from Hayreh* et al.*[14]*

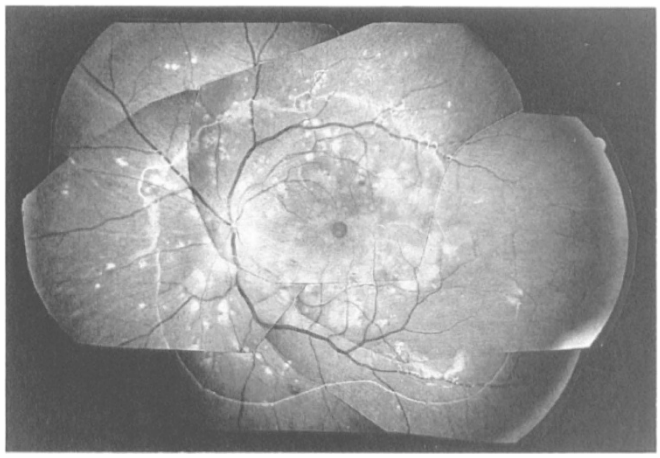


Fig. 8. *Fundus photograph of left eye of a hypertensive rhesus monkey with systolic BP 198 mmHg. It shows serous retinal detachment (notice demarcation line outlining retinal detachment) with multiple acute focal RPE lesions, foveal cyst and multiple FIPTs (along the retinal arterioles). Reproduced from Hayreh* et al.[16]

On ophthalmoscopy these look white and in the literature have been called 'silver-wire arteries'.

During the early, acute phase of malignant hypertension, the *terminal arterioles* may show two types of change:

1. *Dilatation of terminal arterioles.* This is caused by failure of autoregulation secondary to accelerated hypertension to very high levels. Dilatation resulted in focal breakdown of the blood–retinal barrier and development of FIPTs (see below) – the earliest lesion of hypertensive retinopathy seen in our study.[14]
2. *Occlusion of terminal arterioles.* This resulted in development of inner retinal ischaemic spots (cotton-wool spots) and focal retinal capillary obliteration (see below).[20]

Focal Intraretinal Periarteriolar Transudates (FIPTs)

We discovered this retinal lesion, which is very specific for malignant arterial hypertension.[14] In hypertensive retinopathy due to accelerated malignant arterial hypertension, this is common and one of the earliest retinal lesions. FIPTs are round or oval in shape, varying in size from a pinpoint to about a quarter of the optic disc diameter (Figs. 5a, 6a, 7a, 8). Sometimes they may fuse together to form a larger lesion. FIPTs are dull-white when fresh and later fade away when resolving. They are typically located beside the major retinal arterioles and their main branches posteriorly, and in the deeper retinal layers. On fluorescein fundus angiography, FIPTs show dilatation of the terminal retinal arterioles with focal leaking spots, appearing by the arteriovenous phase of angiography (Figs. 5b, 7b, 9). During the late phase, these fluorescent spots are round in shape and spread out so that some of them may fuse together to form a large patch or a band of retinal staining along the retinal arterioles (Figs. 5c, 9c, 10a), with the original loci of lesions usually still evident as separate hyperfluorescent spots. No capillary obliteration is seen in the FIPTs. Fluorescein leaking spots on angiography appear before the ophthalmoscopically visible lesions. The lesions develop fully in about a week and last for 2 or 3 weeks. FIPTs usually appear in crops. On resolution, they leave no apparent microvascular, ophthalmoscopic or fluorescein angiographic evidence of lesions.

The following sequence of events seems to be responsible for the development of FIPTs:[14] Severe rise of arterial BP → Failure of retinal vascular autoregulation → Focal dilatation of precapillary retinal arterioles → Separation of tight interendothelial cell junctions in the dilated arterioles → Focal breakdown of the blood–retinal barrier → increased permeability of the dilated arterioles to plasmatic macromolecules → Focal accumulation of plasmatic deposits in the retinal tissue → Ophthalmoscopically seen white lesions and fluorescein leaking spots.

FIPTs in the past have been erroneously thought to be cotton-wool spots or precursors of cotton-wool spots;[38] but FIPTs and cotton-wool spots are very different in nature,[14] as the following account shows.

Inner Retinal Ischaemic Spots (Cotton-Wool Spots)

These lesions have been emphasised as an important classical feature of fundus lesions in malignant hypertension ever since the first clinical description of hypertensive retinopathy in 1859.[33] A number of studies have demonstrated that they are due to acute focal ischaemia of the inner retina. In view of that, a scientifically and pathogenetically valid term for this lesion is 'inner retinal ischaemic spot', instead of the common term 'cotton-wool spot' (which simply describes the ophthalmoscopic appearance during the acute phase, without giving any information about its true nature) or 'soft exudates' (this term is absolutely wrong since these are *not* exudative, but ischaemic, in origin).[20]

On ophthalmoscopy, inner retinal ischaemic spots usually are fluffy white focal areas of retinal opacity having irregular polymorphous shapes, frequently with somewhat feathery margins (Figs. 7a, 11, 12, 13a). They are situated mostly in the surface nerve fibre layer of the retina, usually in the posterior pole (within a few disc diameters of the disc), basically in the distribution of the radial peripapillary retinal capillaries,[39,40] and more closely related to the arterioles than to the venules. During the acute phase, they usually bulge slightly forward on the surface of the retina. The characteristic life cycle of an inner retinal ischaemic spot is that it starts as a grey film, expands as a white creamy fluffy cloud and resolves into a dull fragmenting white patch before

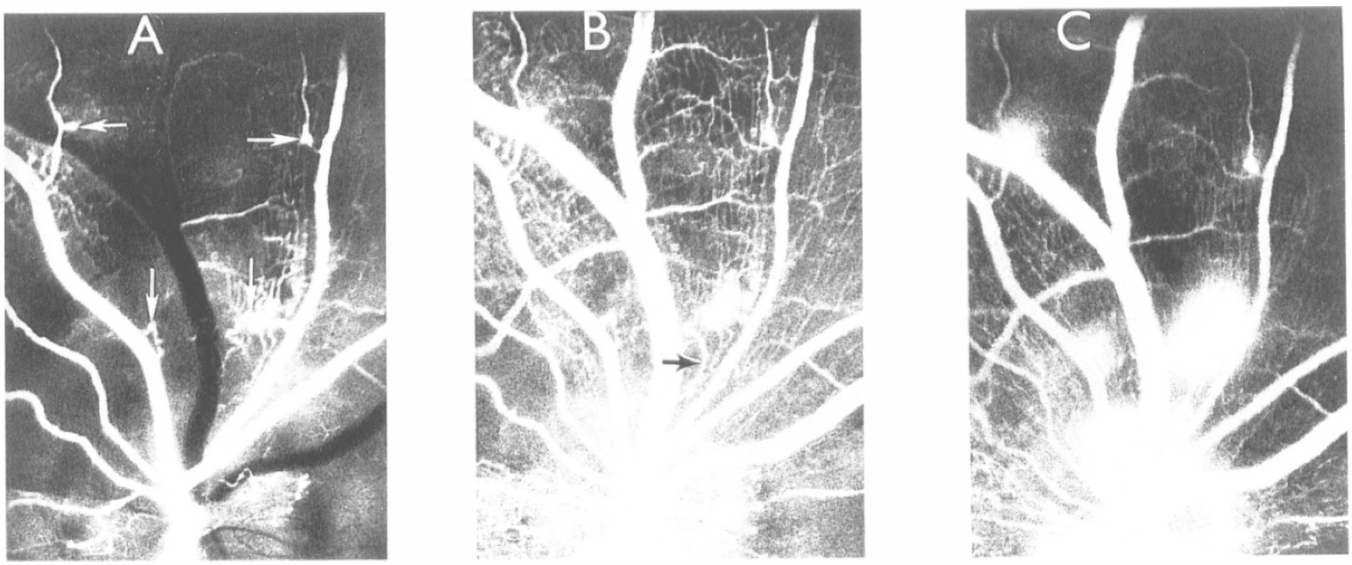


Fig. 9. *Fluorescein angiograms of right eye of a hypertensive rhesus monkey with systolic BP 198 mmHg. Magnified views during retinal arterial (A), late arteriovenous (B) and postvenous (C) phases; note dilated precapillary retinal arterioles at four sites (white arrows) in (A) and progressive fluorescein leakage at those sites, with normal filling of retinal capillaries in (B), which also shows dilated venule draining one leaking spot (black arrow). Reproduced from Hayeh* et al.[14]

disappearing[39] (Figs. 3a, 11b, 13a). On fluorescein fundus angiography, they show retinal capillary non-perfusion in their location, progressively becoming more marked, with usually no corresponding fluorescein leakage (Figs. 3b, 7b, 10, 13b, c). They usually last 3–6 weeks. Finally, on resolution, ophthalmoscopically they leave a normal-looking, transparent retina, often with loss of retinal nerve fibres corresponding to the location of the spots (Figs. 11b, 12), while fluorescein angiography shows permanent focal retinal capillary non-perfusion at that location (Figs. 3b, 10, 13b, c).

As regards the pathogenesis of inner retinal ischaemic spots, our studies[20] showed that they represent foci of acute ischaemia of the inner retina, produced by occlusion of the corresponding terminal retinal arterioles; however, the exact mechanism responsible for the occlusion of terminal retinal arterioles in the distribution of the radial peripapillary capillaries in malignant arterial hypertension is still not clear. We have discussed the subject at length elsewhere.[20]

Retinal Capillary Changes

As discussed above, retinal capillary obliteration is typically seen at the sites of inner retinal ischaemic spots. The retinal capillary obliteration may produce secondary intraretinal microvascular abnormalities (including microaneurysms, arteriovenous shunts around the areas of capillary obliteration, looped convoluted vessels and venous collaterals).[20] In eyes with extensive retinal capillary non-perfusion I have seen development of optic disc and/or retinal neovascularisation.

Retinal Venous Changes

During the acute stages of hypertensive retinopathy in malignant hypertension retinal venous changes are an uncommon finding.[17] In chronic hypertension, however, retinal venous changes are seen fairly frequently and these include venous nipping at the arteriovenous crossings of major retinal vessels, dilatation and tortuosity of major retinal veins proximal to arteriovenous crossing, or central or branch retinal vein occlusion.

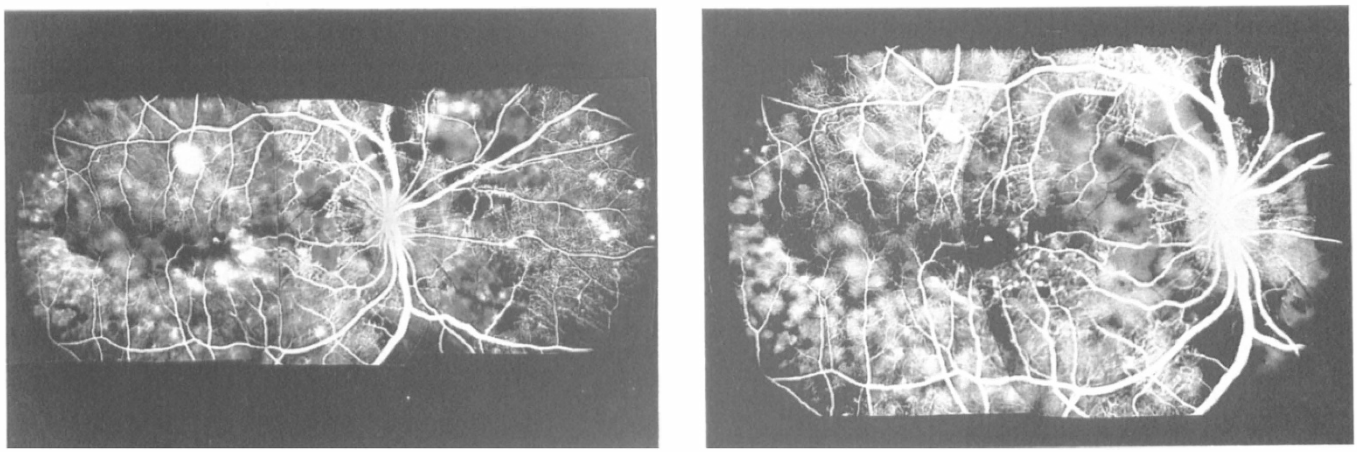
Increased Permeability of the Retinal Vascular Bed

Breakdown of the retina–blood barrier in malignant arterial hypertension is responsible for development of FIPTs,[14] and retinal and macular oedema.[22]

B. Extravascular Retinal Lesions

Retinal Haemorrhages

Retinal haemorrhages have usually been described in the literature as an important, early manifestation of hypertensive retinopathy due to malignant hypertension.[17] Our studies,[17] however, revealed that retinal haemorrhages did not usually constitute either one of the earliest or one of the most conspicuous retinal lesions, but were a minor feature of the retinopathy. We found that haemorrhages were usually situated in the nerve fibre layer and commonly in the distribution of the radial peripapillary retinal capillaries, although they could be located anywhere in the fundus (Figs. 2a, 13a). Their usual occurrence in the distribution of the radial peripapillary capillaries may be due to a combination of the distinctive features of these capillaries[40] and the much thicker nerve fibre layer in their distribution.[17] Optic disc oedema and retinal oedema in the distribution of the radial



(a) (b)

Fig. 10. *Fluorescein angiograms of a hypertensive rhesus monkey with systolic BP 214 mmHg, showing poor choroidal filling and patches of retinal capillary non-perfusion in the distribution of inner retinal ischaemic spots. Fluorescein leaking spots in (a) in the nasal retina represent FIPTs.*

peripapillary capillaries could interfere with the venous outflow from these long, straight, superficial capillaries, and result in development of haemorrhages. The possibility that pathological changes in the capillaries (e.g. ischaemic capillaropathy or other changes due to malignant hypertension) make them liable to haemorrhages cannot be ruled out. Dollery[39] also stated that the haemorrhages arise from the radial peripapillary capillaries, and he postulated that this is because these capillaries have a relatively high intravascular pressure.

Retinal and Macular Oedema

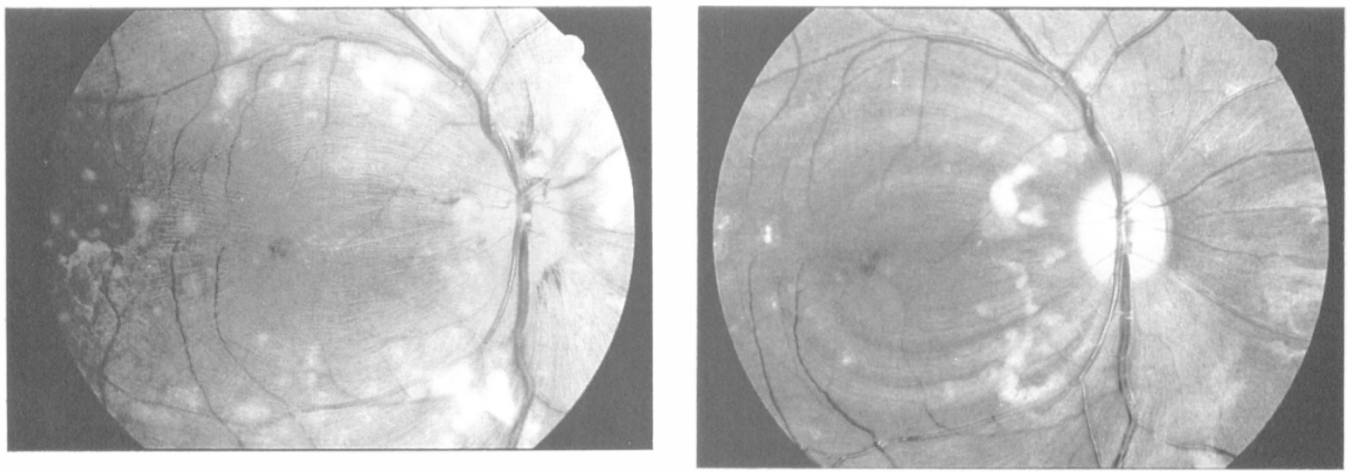
Retinal oedema is a well-known feature of hypertensive retinopathy due to malignant hypertension. It varies markedly in severity from eye to eye and may be generalised or localised (usually in the macular region). Our studies showed macular oedema of variable degree as a common development in malignant hypertension[22] (Figs. 2a, 4a, 5a, 6a, 7a, 8, 11a, 12, 13a, 14). When the macular oedema is marked, it results in secondary macular changes, such as separation of nerve fibres by the interaxonal serous fluid (usually in the retina between the fovea and optic disc), microcystic change, foveal cysts (Figs. 8, 11a, 12, 14), and later on cystoid degeneration (Fig. 6c, d) and rarely whitish subretinal fibrosis. It has been postulated that retinal oedema can be due to autoregulatory failure, resulting in a rise in transmural pressure in the distal arterioles and proximal capillaries, that permits increased transudation of fluid into the retinal tissue.[34,35] Ultrastructural studies by Garner and co-workers[34,35] indicated that intracellular oedema of ischaemic origin is also of importance in the production of retinal oedema in malignant hypertension. Our studies indicated that macular oedema is to a great extent a manifestation of hypertensive choroidopathy[16] by the following sequence of events: Hypertensive choroidopathy → breakdown of the blood–retinal barrier in the retinal pigment epithelium (RPE) → serous retinal detachment → diffusion of subretinal fluid into the retinal tissue → macular oedema.[16] Breakdown of the blood–retinal barrier may also contribute to macular oedema. From this it would seem that macular and retinal oedema may be due to one or more of the factors mentioned above, acting individually or collectively. We have discussed the subject at length elsewhere.[22]

Retinal Lipid Deposits

'Macular star' has been described as a classical feature of hypertensive retinopathy; however, the deposits may not only assume a variety of shapes but also may be seen in other parts of the retina (Figs. 3a, 12, 13a). In our studies[21,22] we found that all eyes with lipid deposits had antecedent macular or retinal oedema or serous retinal detachment. The deposits were constantly evolving, taking months or even more than a year to resolve. Our study suggested that in hypertensive retinopathy the lipid deposits are most probably the result of exudative and/or neural degenerative processes.[21] All the available pieces of evidence indicate that these deposits are composed of lipids. We also found that hyperlipidaemia increased the amount of these deposits. In view of that it is more appropriate to call them 'lipid deposits' than 'hard exudates'.

Retinal Nerve Fibre Loss

Ischaemia in the distribution of inner retinal ischaemic spots (cotton-wool spots) damages the retinal nerve fibres in those locations.[20] The loss of retinal nerve fibres starts to appear as the spots resolve and



(a) (b)

Fig. 11. *Fundus photographs of right eye of a hypertensive rhesus monkey with systolic BP 190–200 mmHg. (a) shows multiple inner retinal ischaemic spots, FIPTs and acute focal RPE lesions, optic disc oedema, macular retinal oedema, and other lesions of hypertensive retinopathy. (b) shows resolution of old inner retinal ischaemic spots and appearance of new ones, with development of multiple areas of nerve fibre bundle loss (seen as dark semicircular bands in the macular region). Reproduced from Hayreh* et al.[15] *(a) and Hayreh* et al.[20] *(b).*

their location corresponds to that of the spots (Fig. 11b). Since the inner retinal ischaemic spots are usually situated in the area of radial peripapillary capillaries,[40] the loss of retinal nerve fibres is most marked in the superior and inferior temporal arcuate areas. We found the nerve fibre loss usually progresses for some time initially.[20] It is possible that some of the nerve fibre loss could also be due to ischaemic damage to the ONH from hypertensive optic neuropathy.[15]

Early and Late Signs of Hypertensive Retinopathy

From this very brief account of hypertensive retinopathy in malignant arterial hypertension, it becomes apparent that the early signs are FIPTs, inner retinal ischaemic spots, a few punctate retinal haemorrhages, and macular oedema. Cystoid macular changes, lipid deposits, retinal arteriolar changes, nerve fibre loss and other retinal changes are late signs of retinopathy.[23] We found no evidence of retinal arteriolar spasm at any stage.[19]

II. Hypertensive Choroidopathy

In contrast to the weighty accumulation of literature on 'hypertensive retinopathy' over the past 137 years,[33] there is practically no significant account of hypertensive choroidopathy. In fact, most of the lesions of hypertensive choroidopathy have erroneously been described under retinopathy. Our studies have shown that, in malignant arterial hypertension, hypertensive choroidopathy is a distinct entity and is clinically as important as hypertensive retinopathy, with a very different underlying pathogenetic mechanism. We have discussed hypertensive choroidopathy in detail elsewhere[11,16] and the following is a brief summary.

In malignant arterial hypertension, endogenous vasoconstrictor agents, including angiotensin II, adrenaline and vasopressin, leak freely from the choriocapillares into the choroidal interstitial fluid. Angiotensin II is one of the most powerful vasoconstrictor agents known, and it also potentiates the vasoconstrictive action of noradrenaline which is released in excessive amounts due to angiotensin stimulating the sympathetic nervous system. The leaked vasoconstrictor agents act on the walls of the choroidal vessels and result in choroidal vasoconstriction and ischaemia. Sympathetic innervation of the choroidal arterioles may further make them susceptible to vasoconstriction. Our fluorescein angiographic[16] and pathological[11] studies showed that choroidal ischaemia initially is of an acute type and later becomes chronic; the effects of the two types of ischemia on the overlying RPE and retina vary. Thus the various lesions seen in hypertensive choroidopathy are due to choroidal ischemia.

Hypertensive choroidopathy lesions are described in detail elsewhere.[11,16] Clinically, these lesions consist of the following:

Choroidal vascular bed abnormalities
Retinal pigment epithelial (RPE) lesions
  Acute focal RPE lesions
  RPE degenerative lesions
Serous retinal detachment

A. Choroidal Vascular Bed Abnormalities

Fluorescein angiography reveals these abnormalities best. We found interference with choroidal arterial circulation one of the earliest invariable findings in hypertensive choroidopathy in malignant hypertension[11,16] (Figs. 4c, 6b, 7b, 10b, 15, 16). There is

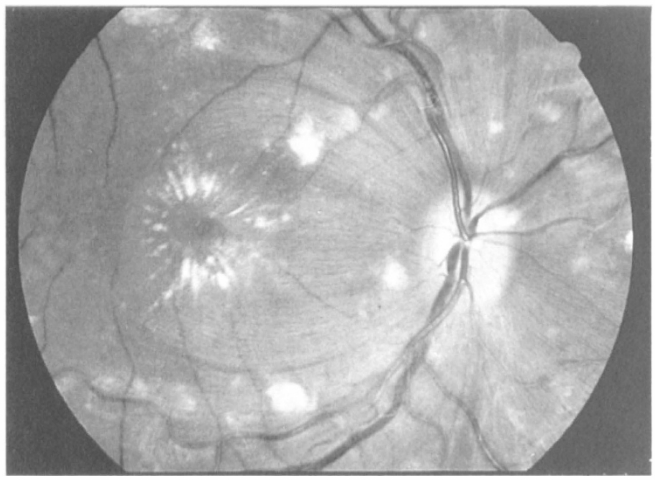


Fig. 12. *Fundus photograph of a hypertensive rhesus monkey on an atherogenic diet showing lipid deposits at the posterior pole. Reproduced from Hayreh* et al.[21]

usually a generalised delayed filling of the choroidal vascular bed, mostly showing a patchy filling pattern, especially marked in the macular or foveal region[16] (Fig. 15). We found a significant ($p<0.01$) correlation between the choroidal circulatory disturbances and the BP level.[16] On ophthalmoscopy, there is evidence of choroidal vascular sclerosis in some eyes, particularly in those associated with extensive RPE degeneration.[16]

Our histopathological studies revealed extensive choroidal vascular abnormalities which could be classified into three stages.[11] In the *acute ischaemic phase* the initial change in the choroidal vascular bed is constriction of arterioles, leading to acute ischaemic changes in the regional choriocapillaris and overlying RPE. During the *chronic occlusive phase* occlusive changes involve choroidal arteries and arterioles, and later on choriocapillaris. In due course, in the *chronic reparative phase*, recanalisation of the choroidal vessels takes place. Arteriolisation of the choriocapillaris, which seems to be a defensive mechanism to withstand the raised systemic BP, also occurs.

B. Retinal Pigment Epithelial Lesions

These are ischaemic in nature and can be further classified into two types:

Acute focal RPE Lesions

Acute severe choroidal ischaemia causes focal infarction of the overlying RPE and the outer retina. Clinically these lesions very often manifest as pale or white, punctate, round, focal, usually pinhead in size, and commonly distributed in groups, some of them associated with focal serous retinal detachment[16] (Figs. 4a, b, 6a, 7a, 8, 11, 14). They are usually situated in the macular region and frequently also elsewhere in the posterior fundus and in the periphery. With time these lesions increase in number. On fluorescein angiography, at this stage, apart from the delayed and generally patchy filling of the choroidal vascular bed (especially marked in the macular or foveal region), there is staining of these lesions during the late phase[16] (Fig. 4d). Pathological studies showed that the initial choroidal arteriolar constriction caused acute focal necrosis of the choriocapillaris and the RPE and focal subretinal exudate.[11]

On routine ophthalmoscopy the acute focal RPE lesions[16] may be confused with FIPTs,[14] but on fluorescein angiography the RPE lesions stain less intensely and their staining persists for a much shorter time than the FIPTs; moreover RPE lesions are subretinal while FIPTs are intraretinal.

RPE Degenerative Lesions

These can be further subdivided into early and late lesions.[16]

Early RPE degenerative lesions. In 2–3 weeks the acute focal RPE lesions develop into focal RPE degenerative lesions. The two look very similar on ophthalmoscopy but fluorescein angiography shows unmasking of the underlying choroidal fluorescence with no late staining of the degenerative lesions (Figs. 6b, 7b, 13c). The acute lesions may become confluent and result in either ill-defined chorioretinal degenerative areas or fairly defined punched-out RPE degenerative lesions (the so-called Elschnig's spots: Fig. 13c). Since the acute lesions have only a short life span and change into degenerative lesions, the latter are far more numerous than the former.

Late RPE degenerative lesions. The degenerative lesions are almost invariably progressive in nature for a long time, so that they are far more extensive than the acute lesions (Figs. 4e, 6d). This would indicate that progressive degenerative lesions are due to persistent chronic choroidal ischaemia, not always preceded by acute lesions. These lesions are widely scattered throughout the fundus, being common in the macular and peripheral regions (the peripheral lesions are usually much more extensive than those in the macular region); the temporal part of the macular region and the temporal part of the peripheral fundus are the most extensively involved areas. On ophthalmoscopy,[16] they are usually made up of polymorphic RPE atrophic areas as well as of diffuse pigmentary change, the latter giving a coarse granular or moth-eaten appearance to the RPE (Figs. 4e, 6c, d). The atrophic lesions may vary from being focal to confluent patches of varying size (e.g. geographic, triangular, irregular). Some eyes may show colloid degeneration of the RPE. In the macular region, these changes may very much resemble those seen in age-related macular degeneration. In some eyes with widespread RPE degen-

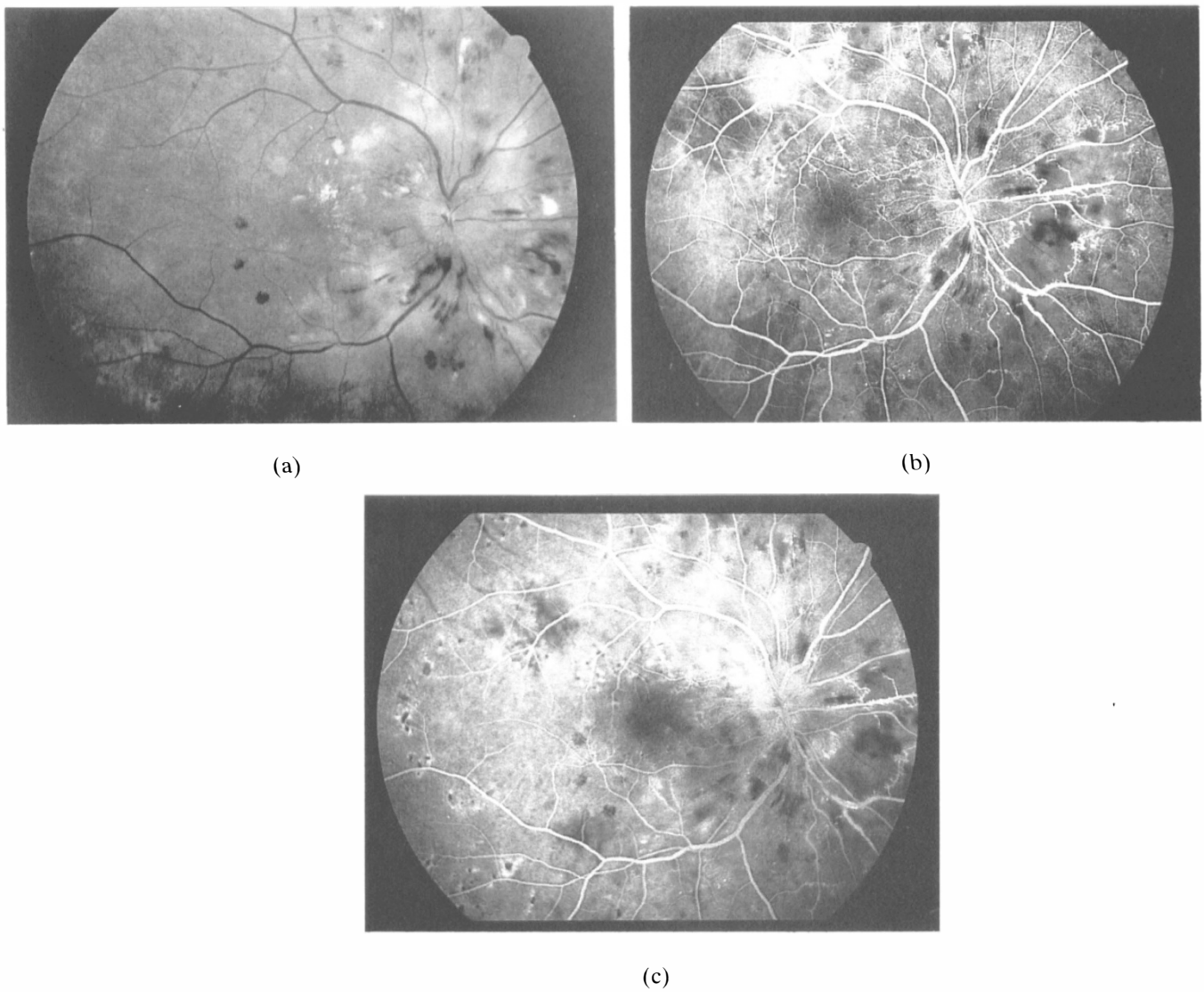


Fig. 13. *Fundus photograph (a) and fluorescein angiograms (b, c) of a 38-year-old man with malignant hypertension. (a) shows optic disc oedema, resolving inner retinal ischaemic spots, retinal haemorrhages, multiple focal RPE lesions (so-called Elschnig's spots), mild retinal and macular oedema with a few fine lipid deposits, and serous retinal detachment in the lower periphery of the fundus (not seen in the photograph). (b) shows markedly delayed and patchy filling of the choroid, patches of retinal capillary obliteration, retinal microaneurysms and other intraretinal microvascular abnormalities; late phase angiogram (c) shows multiple focal RPE lesions – with dark centre and a fluorescent halo around that – and staining of the optic disc and oedematous areas of the retina. Reproduced from* Ophthalmology Annual *(1989) pp. 1-38, by courtesy of Raven Press, New York.*

eration, the overall fundus appearance may be very similar to the late stages of the clinical entity called 'birdshot retinopathy'.

On fluorescein fundus angiography,[16] RPE degeneration is seen much more clearly and more extensively than on ophthalmoscopy because of unmasking of the underlying choroidal fluorescence in the degenerated areas. There is no late staining of these lesions. When the macular region is involved, the angiographic appearance may closely resemble age-related macular degeneration.

Pathological studies[11] reveal that chronic occlusive changes involving the arteries, arterioles and choriocapillaris result in diffuse patchy RPE degeneration and depigmentation, which follows the lobular arrangement of the choriocapillaris.

C. Serous Retinal Detachment

When hypertensive choroidopathy was seen in our studies,[16] macular and/or peripapillary serous retinal detachment of variable degree was almost always seen and was an important and prominent finding (Figs. 5a, 6a, 7a, 8, 14). We found no definite relationship between the development of serous retinal detachment and that of hypertensive retinopathy, indicating that the serous retinal detachment was not secondary to the retinopathy. However, the retina overlying the serous retinal detachment, particularly in the macular region, usually showed

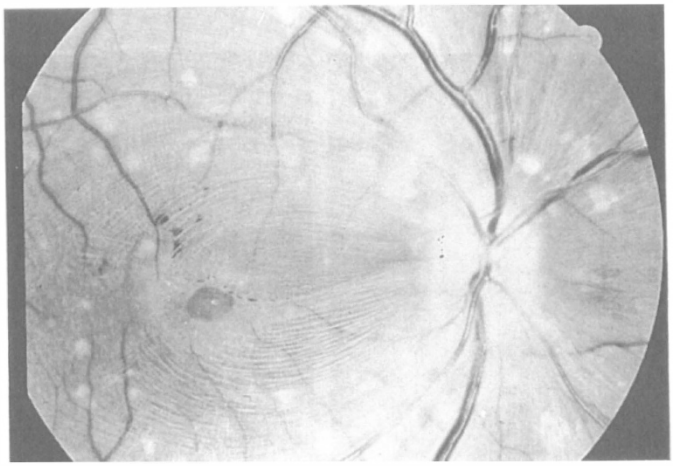
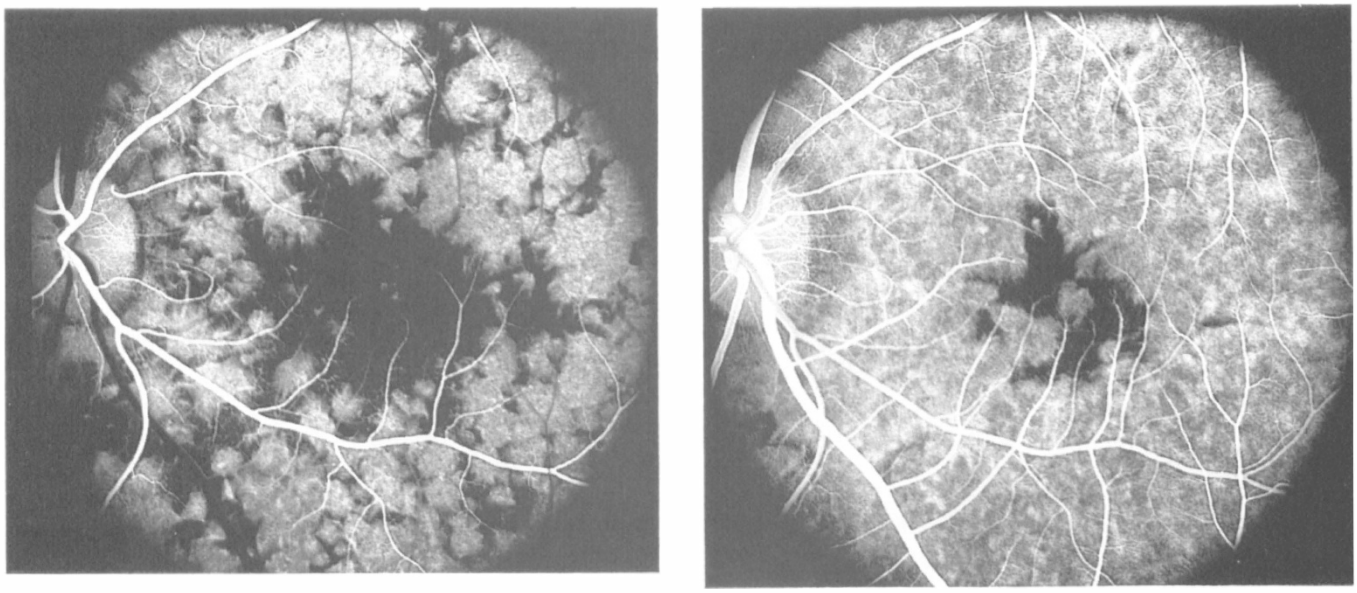


Fig. 14. *Fundus photograph of right eye of a hypertensive rhesus monkey with systolic BP 190 mmHg. Note the optic disc oedema, serous retinal detachment with separation of nerve fibres by oedema, microcystic oedema, foveal cyst and focal RPE lesions (white spots in macular region). Reproduced from Hayreh* et al.[16]



(a) (b)

Fig. 15. *Fluorescein fundus angiograms of the left eye of a hypertensive rhesus monkey with systolic BP 205 mmHg, during retinal (a) and late venous (b) phases, show marked delay in filling of the submacular choroid. Reproduced from Hayreh* et al.[16]

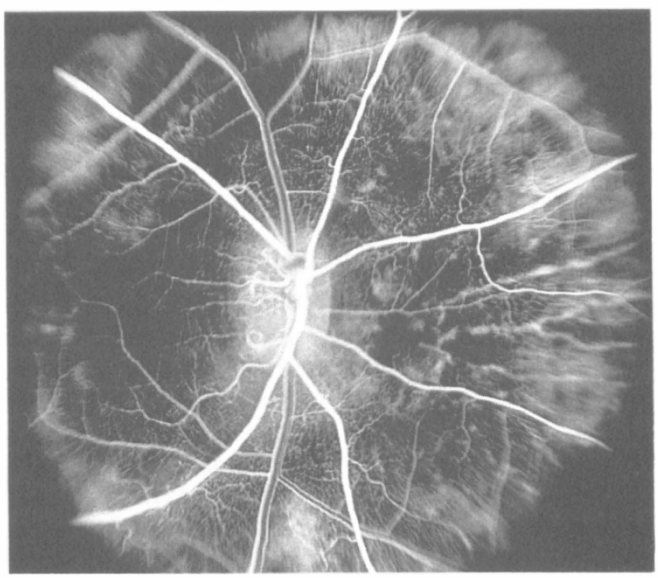


Fig. 16. *Fluorescein angiogram of right eye of a hypertensive rhesus monkey with systolic BP 170 mmHg showing marked choroidal filling defect, particularly in the peripapillary choroid. Reproduced from Hayreh* et al.[15]

frank oedematous changes, consisting of macular retinal oedema, frequently with microcystic changes, and (in a quarter of the cases) a prominent foveolar cyst (Figs. 8, 14). The subretinal fluid is usually clear initially but becomes progressively turbid, opaque, white and exudative in marked cases with time, most notably in the foveal zone. Peripheral retinal detachment, when present, is usually bullous and may extend 360°, and may lead to total retinal detachment, with subretinal fluid shifting with change of position of the head. The serous retinal detachment resolves spontaneously in due course.

All the evidence in our studies[11,16] shows that ischaemia of the RPE causes breakdown of the normal blood–retinal barrier in RPE, resulting in leakage of fluid, proteins and other materials from the choroid, through the RPE, into the subretinal space, and production of serous retinal detachment.

III. Hypertensive Optic Neuropathy

In the past, the occurrence of optic disc oedema in malignant arterial hypertension was invariably thought to point to a poor prognosis for the survival of the patient. For example, according to the Keith-Wagener-Barker[41] classification of hypertensive fundus changes, survival time for patients with optic disc oedema (i.e. 'grade IV hypertensive retinopathy') was only 4½ months, and Kincaid Smith[42] found that 50% of the untreated patients in this group died within 2 months and 90% within a year. Therefore, the presence of optic disc oedema in malignant hypertension came to be regarded as an ominous prognostic sign. However, McGregor *et al.*,[43] on the basis of their clinical studies in 96 consecutive patients with hypertensive retinopathy and optic disc oedema, found that optic disc oedema was not related to survival, and they concluded that optic disc oedema is an unreliable physical sign and does not deleteriously influence the prognosis in hypertensive patients. They further held that optic disc oedema should no longer be regarded as a necessary feature of malignant hypertension. Our studies support the views of McGregor *et al.*[43]

Apart from this clinical controversy on the importance of optic disc oedema in malignant hypertension, its nature and pathogenesis have also remained contentious. Our studies on the subject provide important insight into the clinical course of optic disc oedema, its evolution and other manifestations, and its pathogenesis.[12,15]

Hypertensive Optic Neuropathy Lesions

Our studies[15] showed that the initial optic disc change in malignant hypertension is oedema (Figs. 2a, 4a, 5a, 8a, 11a, 12, 13a, 14) which, on ophthalmoscopy, is indistinguishable from optic disc oedema seen in many other conditions, such as raised intracranial pressure. Fluorescein fundus angiography at this stage usually shows a variable amount of choroidal filling delay or choroidal circulatory disturbance in the posterior pole (Figs. 10b, 16). On follow-up the disc oedema usually resolves and is frequently followed by a variable degree of optic disc pallor (Figs. 3a, 4e, 6c, d, 11b). Our pathological studies[12] revealed that optic disc oedema in these eyes was due to axonal hydropic swelling secondary to ischaemia, followed by loss of axons and gliosis, so that ischaemia seemed to play a major role in the pathogenesis of hypertensive optic neuropathy.

Pathogenesis of Hypertensive Optic Neuropathy

This has long been a highly controversial subject, and an enormous amount of literature has accumulated on it.[15] We have discussed the topic at length elsewhere.[15] Very briefly, the various explanations of the pathogenesis of optic disc oedema in malignant hypertension cna be divided into four categories: (i) optic disc oedema due to raised intracranial pressure, (ii) optic disc oedema similar to hypertensive encephalopathy, (iii) optic disc oedema as a part of hypertensive retinopathy, and (iv) optic disc oedema that is ischaemic in nature. The pathological findings in our studies[12] showed that hypertensive optic neuropathy is ischaemic in nature. Similarly, we found clinical patterns of optic disc oedema and optic disc changes in malignant hypertension to be similar to those of anterior ischaemic optic neuropathy (AION).[15]

Mechanism of Ischaemia of ONH in Hypertensive Optic Neuropathy

To understand this, the following very important facts must be borne in mind: (i) The primary source of blood supply to the ONH is the posterior ciliary artery circulation, and peripapillary choroid is the major source.[28] (ii) There is no blood–optic nerve barrier because the choroidal interstitial fluid diffuses into the ONH from the peripapillary choroid through the border tissue of Elschnig.[31] (iii) As discussed above, concerning the pathogenesis of hypertensive choroidopathy, angiotensin II and other endogenous vasoconstrictor agents leak freely into the choroidal interstitial fluid. (iv) In the discussion of hypertensive choroidopathy, marked vasoconstriction of the choroidal arteries and arterioles, and consequent choroidal ischaemia, have been stressed. As a part of hypertensive choroidopathy, the peripapillary choroid also develops marked vasoconstriction and vaso-occlusive changes and consequent ischaemia in its distribution.

From this brief discussion it is evident that ONH ischaemia of variable degree is produced in malignant hypertension by a combination of the following two factors:

1. *Involvement of the peripapillary choroid by vasoconstriction and vaso-occlusive changes* (Fig. 16). Since peripapillary choroid is the main source of blood supply to the ONH,[28] these changes would secondarily cause ischaemia of the ONH.

2. *Diffusion of angiotensin II and other endogenous vasoconstrictors into the ONH from the peripapillary choroid.* These agents would produce vasoconstriction of the blood vessels in the ONH by their direct action, resulting in ischaemia.

Further evidence that these two mechanisms are responsible for hypertensive optic neuropathy is the finding of our studies[13] that there was no significant difference between the time of onset of hypertensive choroidopathy and optic neuropathy, whereas hypertensive retinopathy appeared significantly ($p<0.01$) earlier than both.

Classification of Hypertensive Fundus Changes

Since 1939 a large number of clinical classifications and methods of grading hypertensive fundus changes have been put forward,[41,44–48] the most widely used one being that of Keith, Wagener and Barker.[41] In the light of our current understanding of the subject, I recently discussed at length[23] the multiple limitations in this and other classifications.

From the previous discussion of the normal anatomical and physiological properties of the retinal, choroidal and ONH vascular beds, and of the pathophysiologies of malignant arterial hypertension and of hypertensive retinopathy, choroidopathy and optic neuropathy, it becomes evident that various fundus lesions seen in malignant arterial hypertension defy any classification and grading of the type put foward in the past. I strongly discourage grading hypertensive fundus changes, but recommend giving a descriptive account of the individual fundus lesions revealed by ophthalmoscopy and fluorescein fundus angiography. That is far more informative and useful in follow-up and estimation of severity of hypertensive fundus changes than the various arbitrary grades advocated. Different hypertensive fundus lesions in a patient may have different severities, as indicated by our studies. Moreover, because of differences in the pathogenesis of the various lesions in hypertensive fundus changes, different lesions have different degrees of significance.

Association of Arterial Hypertension with Other Ophthalmic Diseases

Systemic arterial hypertension, particularly chronic arterial hypertension, has a well-recognised and important association with a variety of severely blinding ocular and ONH vascular disorders, including AION,[4,8] glaucomatous optic neuropathy,[5,7,9,27,49–53] retinal arterial and venous occlusive disorders, and retinal macroaneurysms. It produces these disorders far more often than fundus lesions. All these disorders are multifactorial in nature and we have discussed elsewhere[10] the role of arterial hypertension in ocular and ONH ischaemic disorders. Thus arterial hypertension plays an important part in development of ocular and ONH lesions.

SYSTEMIC ARTERIAL HYPOTENSION

An abnormal degree of systemic arterial hypotension may occur in a variety of conditions. It may be due to excessive blood loss or shock from any cause. Aggressive antihypertensive therapy with very potent antihypertensive drugs currently available is emerging as a fairly common cause of arterial hypotension; this is because it is almost universally believed, by both the lay public and the medical profession, that the lower the BP the better it is for the patient. Another common cause of arterial hypotension is an abnormal drop in BP during sleep (i.e. nocturnal arterial hypotension), particularly in those on antihypertensive therapy. Recent studies have suggested that arterial hypotension can have fairly serious deleterious effects, particularly in hypertensives and/or those with impaired blood flow autoregulation. It has been proposed that one of the factors responsible for that is the 'J-shaped curve phenomenon'.

'J-shaped Curve Phenomenon'

It is well known that when arterial hypertensives are treated with antihypertensive agents, lowering BP reduces cardiovascular mortality and morbidity. But recent studies have shown that if diastolic BP is lowered below a critical level, the beneficial effect is lost and the mortality and morbidity start to increase again. This has been called a 'J-shaped curve phenomenon'.[54–58] In a recent critical review[58] of 13 studies involving more than 48 000 subjects, it was found that the critical therapeutic threshold point for diastolic BP was 85 mmHg, because at 75 mmHg diastolic BP the rate of cardiac events was twice that seen at 85 mmHg. This data analysis also revealed that the extent of the fall in diastolic BP is important because the turning point of the J-shaped curve occurred at a drop in diastolic BP of 17–19 mmHg.[59,60] It is known that in hypertensives a large and sudden reduction in BP causes vascular accidents, because the BP has fallen below the autoregulation range. As discussed earlier, in arterial hypertension the range of autoregulation shifts to higher levels to adapt to high BP,[15] but such an adjustment makes such a person correspondingly less tolerant to low BP (Fig. 1), resulting in vascular accidents – cardiovascular, cerebrovascular and ocular. The 'J-shaped' phenomenon may occur not only therapeutically but also biologically.[61]

Nocturnal Arterial Hypotension

Recently we have systematically investigated this subject because in my clinical studies conducted during the past 25 years, I have found development of visual loss during sleep in many patients with AION, as well as in some patients with central retinal vein occlusion, central retinal artery occlusion and ocular ischaemia,[6,26,62–64] with the patient discovering the visual loss on waking in the morning. More than 70% of patients in our series of over 900 patients with AION discovered the visual loss on waking.[8,62–64] This has also been observed by me in some patients with chronic optic disc oedema (usally from idiopathic intracranial hypertension). All this means that some important event is happening during sleep which precipitates the development of these ocular vascular accidents. In 1974 I postulated that nocturnal hypotension is probably an important factor in the development of AION.[62] In the other conditions I also suspected that nocturnal arterial hypotension may be the culprit. However, until very recently we did not have the technology to study that hypothesis. With the recent development of ambulatory BP monitoring equipment, it is now possible to test the hypothesis by non-invasively monitoring BP every few minutes around the clock, while a person leads a relatively normal life.

We have systematically investigated nocturnal arterial hypotension in about 300 patients with AION and glaucomatous optic neuropathy and several other ocular vascular disorders since 1989, using ambulatory BP monitoring (recording BP every 10 minutes) over a 24 hour period.[10] In our ambulatory BP monitoring study,[10] hourly average BP showed a significant ($p<0.0001$) drop in mean systolic (26%) and diastolic (33%) BPs at night. Fig. 17 shows the overall pattern of mean hourly systolic and diastolic BP over a 24 hour period, with the drop in BP during the night, among normotensives and untreated hypertensives. A comparison of the BP patterns in AION, normal-tension glaucoma and primary open angle glaucoma showed a significantly lower mean night-time diastolic BP (for hourly average BP $p = 0.0028$, and for individual BP readings $p = 0.0080$) in normal-tension glaucoma compared with AION. The mean percentage drop in diastolic BP was significantly greater in normal-tension glaucoma than in AION (for hourly average BP $p = 0.0044$, and for individual BP readings $p = 0.0170$), with no statistically significant difference on comparing primary open angle glaucoma with AION and normal-tension glaucoma – although there is a definite trend for lower diastolic BP in normal-tension glaucoma as compared with primary open angle glaucoma (for hourly average BP $p = 0.0963$, and for individual BP readings $p = 0.0555$). Arterial hypertensives on oral hypotensive therapy showed a significant association between progressive visual field deterioration and nocturnal hypotension, particularly in AION. Intraocular pressure showed no significant correlation with visual field deterioration in any of these conditions.

That BP falls considerably during sleep has been known since 1964[65] and demonstrated by many ambulatory BP monitoring studies.[66] We have discussed the subjects of nocturnal arterial hypotension and ambulatory BP monitoring in detail elsewhere.[10] While a fall in BP during sleep (even during a sound nap during the day) is a physiological phenomenon, it is aggravated under certain circumstances. For example, it has been shown that arterial hypotensive drugs can aggravate the nocturnal arterial hypotension. For example, Floras,[67] in a study of 34 hypertensive patients on systemic beta-blockers, found during sleep a diastolic BP of $\leqslant$50 mmHg in 11 patients compared with only 2 before treatment. In a number of his treated patients, mean diastolic BP $\leqslant$30 mmHg was recorded during 7 hours of sleep and 30–40 mmHg during 10 hours of sleep – the lowest mean hourly diastolic BP during sleep before treatment was 48 mmHg.

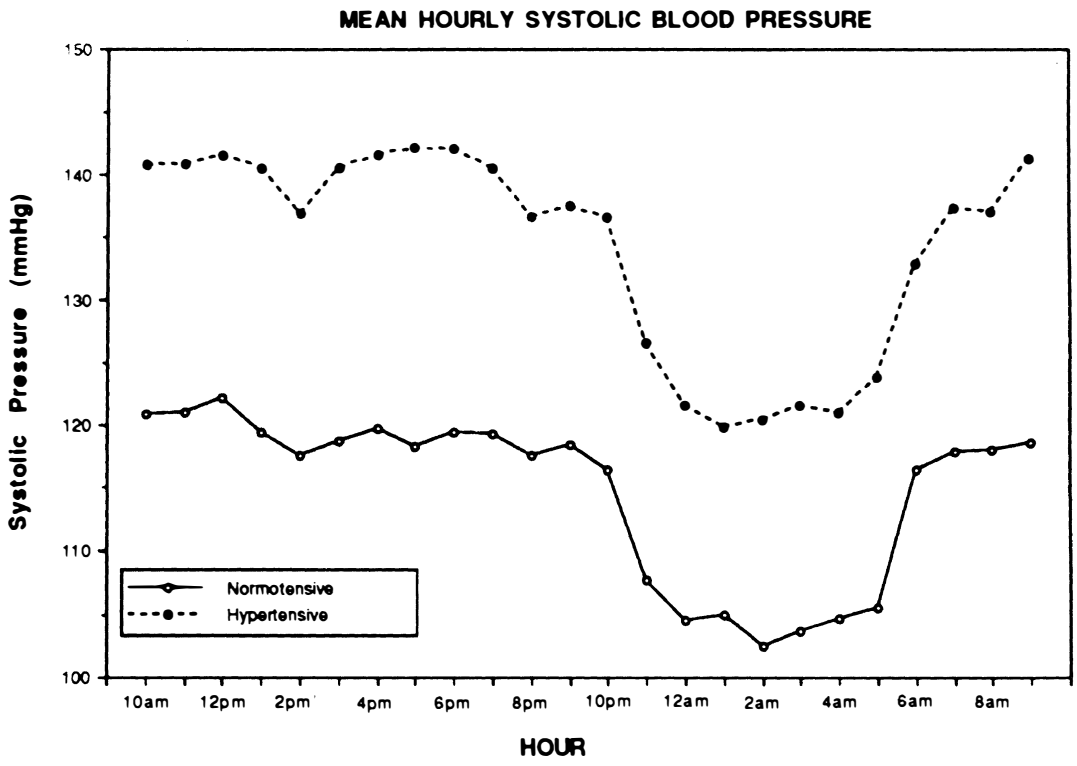
Role of Nocturnal Arterial Hypotension in the Pathogenesis of Various ONH and Ocular Vascular Disorders

To comprehend this, it is essential to understand that these disorders are multifactorial in nature and that the risk factors can be broadly classified into two categories:

1. *Predisposing factors.* These make the ONH and/or other ocular vascular beds susceptible to ischaemic/occlusive disorders. These factors may be systemic and/or local ocular, including old age, arterial hypertension, diabetes mellitus, raised intraocular pressure, arteriosclerosis, atherosclerosis, vasospasm, deranged autoregulation, internal carotid artery disease, low ophthalmic artery pressure, haematological abnormalities, disorders of vasoactive agents produced by vascular endothelium, and a host of other known and unknown factors.

2. *Precipitating factor(s).* A precipitating factor acts as the final insult to produce ischaemic/vascular occlusive disorder, although on its own it may not produce any problem. Nocturnal hypotension may be one such factor.

In such a multifactorial scenario, a particular factor or combination of factors may be present in one case and not in another, or a factor may play a major role in one case and only a subsidiary role in another. Moreover, the roles of various factors may vary, with some as predisposing factors and others as precipitating ones in one group of patients and vice versa in another. Thus each patient may have a unique combination of systemic and local factors responsible



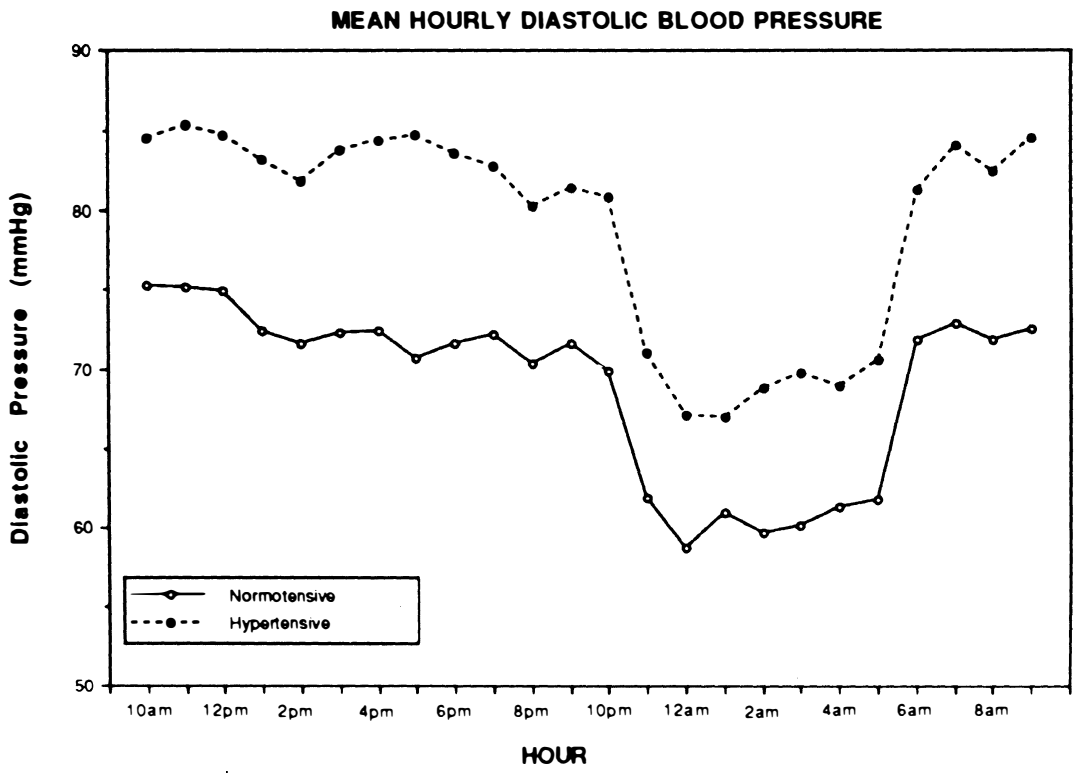


Fig. 17. *Mean hourly systolic and diastolic BPs over a 24 hour period in patients with normal BP (normotensive) and hypertension (hypertensive).*

for finally producing an acute ONH ischaemic or ocular vascular occlusive disorder; the common tendency to blame only one factor in these disorders is erroneous.

A. ONH Ischaemic Disorders

The pathogeneses of AION and glaucomatous optic neuropathy – two very prevalent and blinding disorders - have been highly controversial, particularly that of glaucomatous optic neuropathy. Although nocturnal arterial hypotension is a physiological phenomenon, our findings[10] suggest that it may contribute to ONH damage in patients susceptible due to pre-existing vascular insufficiency produced by other local and/or systemic risk factors. These factors include poor blood supply of the ONH (as revealed by many fluorescein angiographic studies in glaucomatous optic neuropathy[5,7,68] and AION[4,69,70]), deranged autoregulation of blood flow in the ONH (from hypertension, ageing, arteriosclerosis and other unknown causes),[7,25,28] vasospastic disorders,[4,7,71,72] location of posterior ciliary artery watershed zone(s) in relation to the ONH,[28,70,73] internal carotid artery disease, low ophthalmic artery pressure, systemic arteriosclerosis and arteriosclerotic changes in the ONH vessels, systemic hypertension and associated changes in the ONH vasculature, diabetes mellitus, elevated intraocular pressure, and many other factors known and unknown. Our hypothesis is that in such a multifactorial situation with the ONH susceptible to vascular insufficiency, nocturnal hypotension, although not the primary factor in the development of ONH ischaemia, may act as 'the straw that breaks the camel's back'. Thus, nocturnal hypotension in the presence of other vascular risk factors may reduce the ONH blood flow below a critical level, and thereby may play a role in the pathogenesis of AION and glaucomatous optic neuropathy.

Anterior Ischaemic Optic Neuropathy

In an ONH predisposed to ischaemia (due to the multiple factors discussed above[10]) a fall in BP during the night fall of perfusion pressure below a certain critical limit in the ONH vascular bed hypoperfusion or non-perfusion of the ONH ONH ischaemia. Acute ischaemia of a marked degree would result in AION. This is suggested by the fact that classically patients with AION discover visual loss on waking in the morning. Our study also suggests that nocturnal hypotension may be a factor in the progressive visual field deterioration seen in AION eyes (see above).

Glaucomatous Optic Neuropathy

There is strong evidence that this is due to vascular insufficiency in the ONH.[5,7,9] It has been reported that a low systemic BP favours the occurrence of visual field defects or development of greater field loss at any intraocular pressure,[52,74–78] particularly a low diastolic BP.[79] In normal-tension glaucoma there is progressive glaucomatous ONH damage, although the intraocular pressure is always normal. In a susceptible ONH, the findings in this study[10] suggest that recurrent nocturnal hypotension may be a factor in the development and progression of normal-tension glaucoma. This may also be true in patients with primary open angle glaucoma, in combination with the raised intraocular pressure. Our study[10] provides evidence suggestive of that. Recently other studies on ambulatory BP monitoring have also shown that nocturnal arterial hypotension may be a risk factor in glaucomatous optic neuropathy.[80]

Chronic Optic Disc Oedema

In chronic optic disc oedema there is swelling of the axons and interstitial oedema.[81] These changes compress the fine vessels lying among them in the prelaminar region and that makes the ONH susceptible to ischaemia.[82,83] In such an ONH, a fall in perfusion pressure below the critical levels from nocturnal hypotension would result in progressive ONH ischaemia and visual loss.

B. Ocular Vascular Occlusive Disorders

Nocturnal hypotension may play an important role in the pathogenesis of a number of other ocular vascular occlusive disorders as well, as is suggested by clinical studies in our Ocular Vascular Clinic during the past 20 years.

Conversion of Partial Arterial/Venous Thrombosis to Complete Thrombosis

Fall in perfusion pressure produced by nocturnal hypotension may convert a partial thrombosis in the central retinal vein, in the central retinal artery or in the posterior ciliary artery (from giant cell arteritis) to complete thrombosis because of poor, sluggish circulation produced by the fall in perfusion pressure. Sluggish circulation is an important factor in progression of thrombosis.

Central Retinal Vein Occlusion

A rise in retinal venous pressure from thrombosis of the central retinal vein reduces the perfusion pressure in the retinal vascular bed to a variable degree, resulting in a variable degree of stasis of retinal blood flow. Nocturnal hypotension, by lowering the arterial pressure, would further reduce the perfusion pressure. A fall in perfusion pressure below the critical level from nocturnal hypotension may lead to markedly sluggish retinal circulation or even no retinal blood flow during sleep. This would convert a partial central retinal vein occlusion to

complete central retinal vein occlusion (see above), or convert a non-ischaemic central retinal vein occlusion to an ischaemic type.[84] This may be responsible for a certain proportion of patients with central retinal vein occlusion first noticing visual deterioration or marked worsening of vision in the morning.

Ocular Ischaemic Syndrome

In eyes with poor perfusion pressure from stenosis or occlusion of the internal carotid or ophthalmic artery, a further fall in perfusion pressure below a certain critical limit from nocturnal hypotension has been seen by us to cause a collapse (but not a permanent, organic occlusion) of retinal, choroidal and/or ONH vascular bed and ischaemia.[26] Such a patient may wake up in the morning with severe visual loss and clinical findings of central retinal artery occlusion, AION and/or choroidal ischaemia, but fluorescein fundus angiography may reveal reasonable circulation because of the return of perfusion pressure to a normal level at the time of angiography, in spite of a prolonged but temporary stasis or complete stoppage of the circulation during the period of nocturnal hypotension.

Ocular vascular occlusive and ischaemic disorders are almost always multifactorial in origin. Our ambulatory BP monitoring study[10] suggests that nocturnal hypotension, in the presence of other vascular risk factors, may reduce the ocular blood flow below a critical level, and thereby may play a role in the pathogenesis of a number of these disorders, particularly ischaemic disorders of the ONH. Nocturnal hypotension may be the final insult in a multifactorial situation in these disorders, although on its own in a healthy individual it may have no deleterious effect. This opens a new and important dimension in the understanding and management of these severe, visually disabling diseases.

Management Considerations in Arterial Hypotension and Nocturnal Hypotension

From the above discussion it seems that nocturnal hypotension in the presence of other risk factors plays an important role in the pathogenesis of a number of visually crippling diseases. Naturally the question arises as to what can be done to prevent this from happening. From our study, as well from the evidence in the literature, one important point emerges: aggressive antihypertensive therapy with multiple potent modern medications may be one precipitating factor. Three examples from my own experience will illustrate this.

Case 1

I saw a 55-year-old physician with a history of recurrent episodes of amaurosis fugax in his right eye (up to 16 times a day) for a few days. Examination revealed that he had had AION with visual field defect in the left eye in the past of which he was not aware. He was taking three medications for high BP – two of them 3 times a day. Whenever his BP was measured in his doctor's consulting-room, it was invariably high, notwithstanding all the medication. When his medication was sharply reduced (in the face of marked reluctance on the part of his doctor) the episodes of loss of vision stopped within 24 hours. Ambulatory BP monitoring evaluation without any medication at all revealed that he *did not* suffer from arterial hypertension and did not really require *any* medication. He simply suffered from 'white coat hypertension' caused by anxiety. I have now followed him for about 3 years without any further problem. If this patient had kept on with the regimen of medicines he was taking, he would have developed AION or other ocular ischaemic disorders in his right eye or both eyes and suffered additional visual loss.

This case illustrates very well the unreliable nature of routine clinic cuff BP measurements, which may

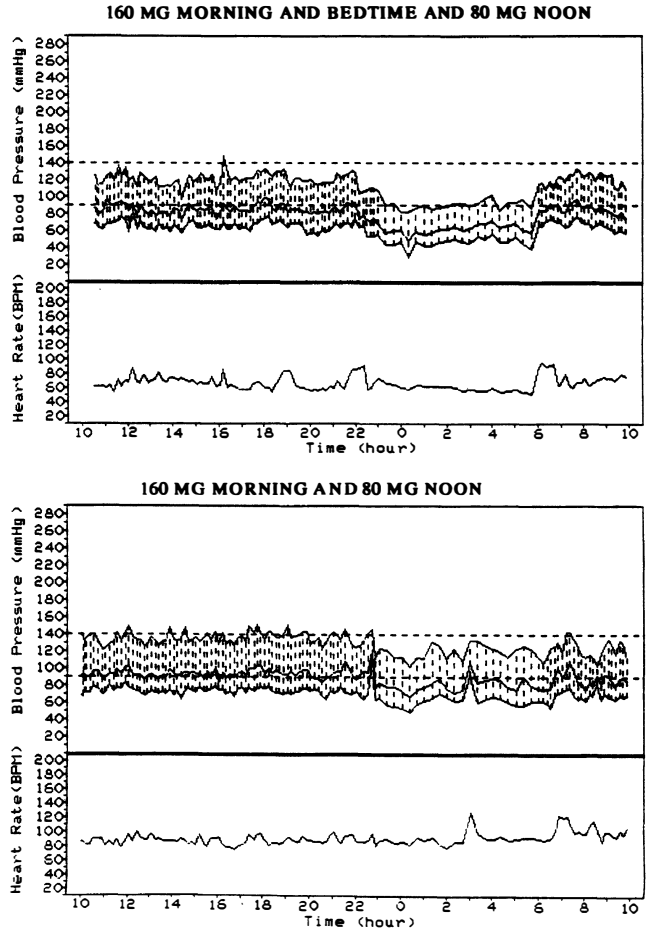


Fig. 18. *Ambulatory BP and heart rate monitoring records over a 24 hour period in a patient with two regimens of verapamil, as indicated on the chart. The upper record shows a marked degree of nocturnal hypotension.*

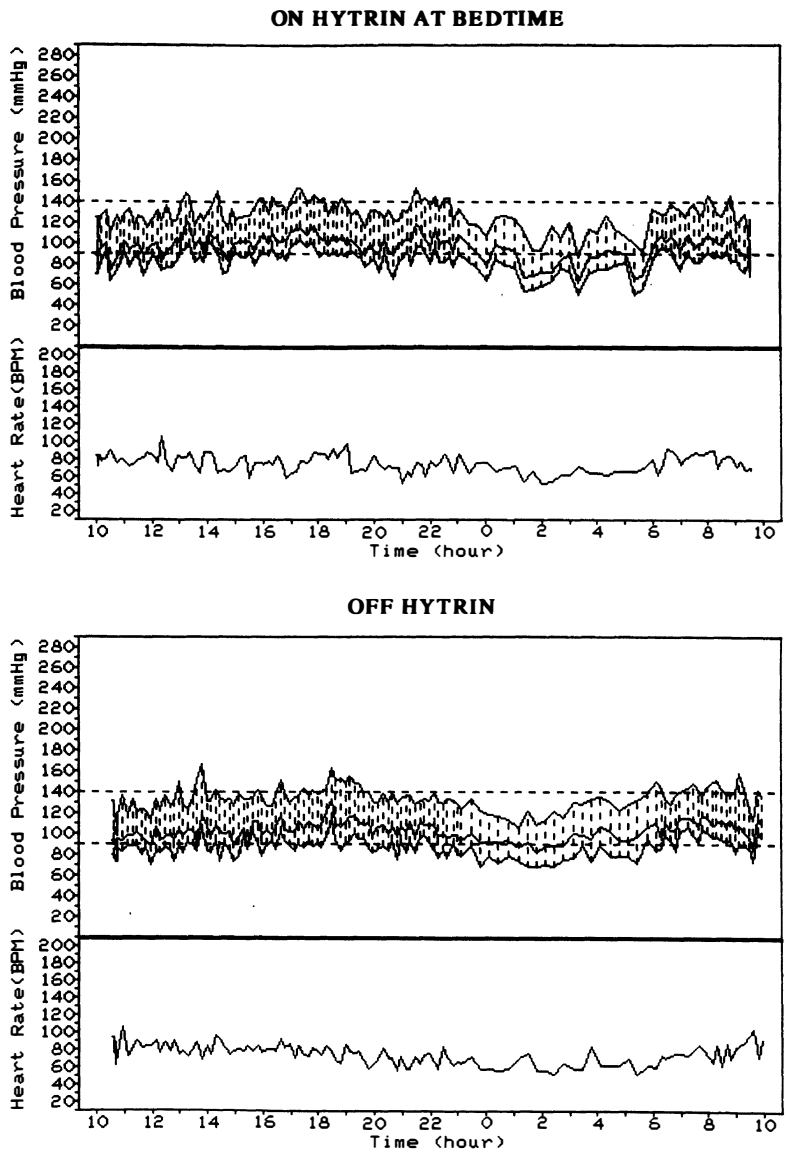


Fig. 19. *Ambulatory BP and heart rate monitoring records over a 24 hour period in a patient with and without Hytrin (terazosin hydrochloride) as indicated on the chart. The upper record shows a marked degree of nocturnal hypotension.*

completely mislead the physician. We know now that routine clinic cuff measurement of the BP usually gives significantly higher readings than ambulatory BP monitoring.[10] In some patients anxiety causes 'white coat hypertension', thereby leading the physician to prescribe more and more unnecessary antihypertensive drugs, with possibly disastrous results.

Case 2

I saw a 63-year-old woman who for 6 years had been on verapamil, a calcium-channel blocker, for migraine (160 mg in the morning and evening and 80 mg at noon). She had started to develop normal-tension glaucoma. Ambulatory BP monitoring, while on this regimen of treatment, showed marked nocturnal hypotension with a systolic BP during sleep of about 80 mmHg and diastolic of about 40 mmHg (as shown in the upper graph in Fig. 18). The lower graph in Fig. 18 shows the pattern of BP after she stopped the evening dose, with marked improvement in nocturnal hypotension. She has not shown any further progression in her glaucoma.

Case 3

I followed a 77-year-old man with stable primary open angle glaucoma for several years. Then he was started on Hytrin (terazosin hydrochloride) for his prostate enlargement; with that he started to have progressive visual field deterioration. On ambulatory BP monitoring he was found to suffer from fairly marked nocturnal hypotension with hytrin (Fig. 19, upper graph). On stopping Hytrin there was much

less marked nocturnal hypotension (Fig. 19, lower graph).

Cases 2 and 3 illustrate the point that drugs such as beta-blockers, calcium-channel blockers, angiotensin converting enzyme inhibitors, terazosin, amitriptyline hydrochloride and allied groups of drugs, given to normotensive patients for a variety of systemic conditions, may produce marked nocturnal hypotension and associated ocular problems. Thus it is vital for ophthalmologists to find out what systemic medications a patient is on. This also illustrates the point that it is the patient who comes to consult an ophthalmologist and not an eye, retina or optic nerve!

These three cases are not isolated examples. About 90% of our patients had diastolic hypotension during the night because of physiological nocturnal hypotension; this indicates that the vast majority of patients do not need any therapy at bedtime to control their BP during the night. In view of this, taking hypertensive medication at bedtime or in the evening is not only usually unnecessary but puts the patient at risk of systemic and/or ocular damage. Not infrequently I have come across cases where patients on oral arterial hypotensive therapy complained of orthostatic hypotensive symptoms or other hypotensive side-effects during the day to their physicians, who advised them to take their medication before going to bed. While this may minimise some other bothersome side effects of BP medication, it is clearly bad advice because it may cause marked nocturnal hypotension in hypertensives which may produce the 'J-shaped curve' phenomenon discussed above, with associated morbidity.

I therefore strongly recommend that when a patient is at risk of developing ocular and ONH ischaemic and vascular disorders because of, for example, (a) AION or history of AION in one eye,[63,64] (b) active giant cell arteritis,[64,85] (c) normal-tension glaucoma, (d) non-ischaemic central retinal vein occlusion,[84] (e) occlusion or severe stenosis of internal carotid artery,[26] (f) low central retinal artery pressure[26] or (g) chronic optic disc oedema,[83] the treating physician should be made aware of the potential risks of intensive arterial hypotensive therapy, particularly in the evening.

CONCLUSIONS

This brief discussion shows that arterial hypertension and hypotension play an important role in either the development or the progression of a number of common, visually crippling disorders. With the development of very potent hypotensive agents for treatment of hypertension, arterial hypotension (particularly nocturnal hypotension) is increasingly emerging as an important cause of visual disorders. In such patients, ophthalmologists need to communicate their concern to the treating physicians so that they are made aware of possible ophthalmic complications of systemic therapies for arterial hypertension.

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