BLOOD FLOW TO THE RETINA AND OPTIC NERVE REMAINS CONSTANT OVER A RANGE OF ELEVATED INTRAOCULAR PRESSURE OR MEAN ARTERIAL PRESSURE, INDEPENDENT OF SYMPATHETIC ACTIVATION (PRESSURE AUTOREGULATION). IN ADDITION, INCREASED METABOLIC ACTIVITY IN THESE TISSUES PROPORTIONALLY INCREASES BLOOD FLOW (METABOLIC AUTOREGULATION). AT CONSTANT METABOLIC RATE, ALTERED ARTERIAL OXYGEN CONTENT RECIPROCALLY ALTERS BLOOD FLOW, LEAVING TOTAL OXYGEN DELIVERY CONSTANT, WHILE BLOOD FLOW RISES AND FALLS WITH THE ARTERIAL CARBON DIOXIDE TENSION. THESE RESPONSES ARE SIMILAR TO THOSE OF THE CEREBRAL CIRCULATION. HOWEVER, WHILE AGING, ATHEROSCLEROSIS, ARTERIAL HYPOTENSION, AND INDIVIDUAL VARIATION MAY PROFOUNDLY ALTER BLOOD FLOW REGULATION AND PREDISPOSE TO THE DEVELOPMENT OF ILLNESS, THESE FACTORS REMAIN LARGELY UNEXPLORED.

The ability to maintain adequate nutrient supply to a tissue, despite variations in metabolic demand, the driving pressure for blood flow, or the oxygen or carbon dioxide content of blood, is critical to maintenance of normal function. Regulation of nutrient supply to a given tissue involves both systemic controls (eg, sympathetic nervous system activation) and local factors modifying smooth muscle tone.1 In retinal and optic nerve circulation, systemic controls have only a minor influence, while local factors (eg, nitric oxide, prostaglandins, endothelin, and the renin-angiotensin system2) dominate regulation.3 In this review, these local factors will be examined for their control of total blood flow to the retina and optic nerve head. While most readers are aware that autoregulation exists in these ocular tissues, we will critically examine the extent and robustness of that autoregulation. Under which conditions might the circulation to the retina or optic nerve head be compromised? Are there individuals who, even in health, display lesser ability to regulate nutrient supply to the eye, thereby rendering them susceptible to ocular illness? Does age or sex, or coexisting cardiovascular disease, predispose to circulatory deficiencies in the eye? Finally, how are specific eye diseases, which clearly include hemodynamic abnormalities, linked to dysfunctional autoregulation? These questions will help illuminate the interface between physiologic and pathologic processes in hopes that increased understanding can guide development of new treatment modalities.

RETINAL BLOOD FLOW

Pressure Autoregulation

Changes in ocular perfusion pressure (defined as the arterial pressure in the ocular vessels minus the intraocular pressure [IOP], or often calculated as two thirds of the mean arterial pressure minus the IOP) occur routinely in daily life, as mediated by stress- and exercise-induced elevations in mean arterial pressure, by nocturnal reductions in arterial pressure, and by diurnal variation in IOP.3 When changes in perfusion pressure occur, local vascular constriction or dilation causes vascular resistance to reciprocally increase or decrease, thereby maintaining a constant nutrient supply; this constitutes the autoregulatory response.5,6 Because increments in brachial artery pressure match increments in ophthalmic artery pressure, retinal pressure autoregulation is primarily mediated by increases in retinal vascular resistance.8 Of course, the plateau of constant retinal blood flow as perfusion pressure varies is limited. For example, in cats, the upper IOP boundary to constant blood flow (as...
measured with radiolabeled iodoantipyrine 1 125) approached 25 mm Hg of the mean femoral arterial pressure.9,10 Similarly, in monkeys, retinal accumulation of radiolabeled carbon 14C-deoxyglucose was apparent only when IOP approached 20 cm H2O of the mean arterial pressure.11 Using blue-field simulation in healthy eyes, acute IOP elevation up to approximately 30 mm Hg left retinal leukocyte velocity unchanged; the lower limit of the autoregulatory range occurred at 6 to 7 mm Hg.3,12 Augmenting the arterial blood pressure with isometric exercise (ocular perfusion pressure rise 34%) increased retinal blood flow less than 5% (laser Doppler flowmetry), and identical results have been found in dynamic exercise using fluorescein angiography.3,13 In contrast with the apparent breadth of the autoregulatory range in these animal models and in healthy humans, in a patient with an IOP of 47 mm Hg, retinal flow (measured using laser Doppler velocimetry) was reduced to one third of normal, suggesting that human retinal autoregulation fails if IOP approaches within 40 to 45 mm Hg of the mean arterial pressure.14 Given the limitations of blood flow measurement techniques,3,13 the complications imposed by different species, and the influence of general anesthesis, the precise boundaries of the human retinal pressure autoregulatory range remain unclear.

At least 2 major problems remain regarding the pressor regulatory capacity of the retina: (1) Most previous studies have been confined to young, healthy animals or humans, and the effects of aging have not been thoroughly studied. In 4 rhesus monkeys fed an atherogenic diet for more than 12 years,14C-deoxyglucose was taken up by the outer retina substantially more than in younger animals on a normal diet, suggesting that either aging or atherosclerosis enhances retinal glycolytic energy production.14 Total cerebral perfusion (the “set point” for blood flow, defined at normal perfusion pressure) declines with age;17 analogous changes in retinal blood flow with aging (a 30%-50% decline between the ages of 20 and 70 years) have recently been described.30 Aging-induced blood flow reductions at normal ocular perfusion pressure clearly increase vulnerability to retinal ischemia at the borders of the autoregulatory range. (2) Studies of group responses leave open the possibility that certain healthy individuals possess a narrow pressure autoregulatory plateau, thereby increasing their susceptibility to retinal ischemic disease.19 Familial tendencies, or the concordance between twins, in retinal blood flow responses to variable perfusion pressure have not been studied.

Metabolic Autoregulation

The ability to elevate perfusion in response to altered tissue needs, classically defined as metabolic autoregulation, exists in many tissues and is apparently well preserved in the healthy retina.4,13 When flicker stimulation increases retinal metabolic demands in cats or monkeys, retinal blood flow increases,6,10 with the vasodilation locally mediated by nitric oxide release.20 These animal studies using radioactive microspheres or 14C-deoxyglucose leave several important questions unanswered. First, it remains unclear if the human retina responds in like fashion to light and dark; studies using laser Doppler velocimetry suggest that dark adaptation substantially increases human retinal perfusion.21,22 In contrast, studies in pigs and rabbits (using directly measured arteriovenous differences for oxygen and glucose) find an identical metabolic rate in both the light and dark adapted retina.23,24 While these species differences are likely due to the retinal stimulus provided by the laser velocimeter itself,a broader unresolved question concerns the ability of metabolically induced increases in perfusion to match an elevated metabolism. It remains possible (though it has never been approached experimentally) that some conditions of increased retinal energy demand exceed the vasodilatory capacity of retinal vessels, leading to tissue hypoxia. In this context, individual differences, aging effects, and vascular disease might increase the risk for ischemia (perhaps in specific retinal regions) during episodes of elevated metabolic demand.

Response to Oxygen and Carbon Dioxide

More than 40 years ago, it was recognized from fundus photography that breathing pure oxygen caused a vasoconstriction of the larger retinal vessels, and that this vasoconstriction was blunted in patients with diabetes.26-28 More recent work, primarily using laser Doppler velocimetry, has confirmed that retinal blood flow rises and falls in inverse proportion to arterial oxygen content at a fixed arterial PCO2.29,31 In patients with diabetes, this response is diminished in proportion to elevations in blood glucose levels32 and as retinopathy progresses.33,34 In healthy patients, retinal circulation mirrors cerebral circulation, which manifests endothelial-mediated (perhaps via adenosine triphosphate [ATP]-sensitive and Ca++-dependent K+ channels35) vasomotor responses as arterial blood oxygen content varies, providing a constant supply of oxygen.36,37 One notable exception to this rule may occur in premature infants and newborns, in whom susceptibility to hyperoxia-induced retinopathy is elevated.38,39 In newborn pigs, the choroidal (but not the retinal) vasoconstrictor response to hyperoxia is absent.40 Increased nitric oxide synthesis in choroidal resistance vessels in the first few days of life may allow excessive choroidal oxygen delivery while breathing pure oxygen, with subsequent increased oxygen diffusion to the retina.40 Studies in neonatal rats and mice suggest that excessive retinal oxygenation may obliterate vessels by down-regulating vascular endothelial growth factor in immature cells lacking adequate free radical scavenging enzymes.41-44 While these findings suggest that prematurity reduces retinal autoregulation of the oxygen supply, little is known about other clinical conditions that might compromise the capacity to maintain constant retinal oxygenation. For example, it is unknown if persons experiencing arterial hypoxia (eg, patients with chronic lung disease or people who venture to high altitudes) suffer from a reduced retinal oxygen supply.55,56 Also, since aging lowers arterial PCO2,57 it is possible that aging or arteriosclerosis also decreases retinal vasodilatory responses to reduced arterial oxygen.

The decisive factor for cerebrovascular smooth muscle is the arterial carbon dioxide tension; cerebral blood flow rises linearly and steeply over a wide PCO2 range.37 This effect, which is mediated through pH changes
in extracellular fluid surrounding cerebral vascular smooth muscle cells and pericytes and involves both nitric oxide and adenosine actions.46-50 It is well preserved in the retina, where bulk flow varies directly with the PCO₂.51 While the importance of this reflex for retinal perfusion in many diseases is unclear, since few chronic illnesses are characterized by long-term alterations in arterial PCO₂ or pH, there is evidence in neonatal rats that hypercarbia exacerbates the retinopathy of prematurity, perhaps by vasodilating retinal resistance vessels and thereby increasing the partial pressure of oxygen within tissue.52 Carbon dioxide reactivity has long been used to test cerebrovascular hemodynamics, and the loss (or preservation) of retinal carbon dioxide responsiveness may provide insight into both disease mechanisms and potential treatments.53

A summary of major questions regarding retinal blood flow autoregulation is given in Table 1.

### OPTIC NERVE BLOOD FLOW

**Pressure Autoregulation**

 Autoradiographic studies of regional optic nerve head flow in cats find constant blood flow over a range of ocular perfusion pressure.53 Indeed, optic nerve head perfusion in anesthetized cats, measured using laser Doppler flowmetry, increased during moderate reductions in ocular perfusion pressure,55 perhaps in response to increased flicker-induced ganglion cell activity.55 In humans, initial studies find optic nerve head pressure autoregulation: in 7 of 10 healthy subjects, optic nerve head perfusion was constant until acute IOP elevation reached 45 mm Hg, suggesting an autoregulatory pressure plateau at least as broad as that found in the optic retina.56 However, 2 of the 10 subjects in this study involving laser Doppler flowmetry showed no pressure autoregulation, with flow falling linearly with falling ocular perfusion pressure, at least in some portions of the disc.56 It remains unknown if individuals with apparently reduced pressure autoregulatory capacity are in fact susceptible to ischemic disease of the optic nerve. Moreover, despite evidence for marked interindividual variation in the blood supply pattern of the optic nerve head,7-58 the importance of these anatomic differences for optic nerve head pressure autoregulation is unclear.

In cerebral circulation, chronic hypertension shifts the autoregulatory plateau to a higher pressure range,59,60 structural changes in the vascular endothelium enhance the capacity for vasoconstriction. These structural changes reduce the ability to vasodilate when perfusion pressure falls.59,60 Consequently, patients with hypertension are at greater risk for cerebral ischemia during periods of reduced arterial blood pressure.59,60 The possibility that parallel changes occur in the ocular circulation in response to atherosclerosis and hypertension remains unexamined. Such changes could help explain the apparent propensity of older persons to glaucomatous damage under conditions of reduced perfusion pressure.61-63 Epidemiologically, these conditions apparently include both sleep and the use of antihypertensive drugs.62-63 Incidentally, while changes in IOP and mean arterial pressure equally influence calculated ocular perfusion pressure, the two changes may not be equivalent.64 The ability of optic nerve head (or retinal) flow to autoregulate when arterial blood pressure decreases has not been carefully explored.64,65

The effects of aging and atherosclerosis on optic nerve head pressure autoregulation have recently been studied in old monkeys maintained on an atherogenic diet. When subjected to increased IOP that reduced directly measured ocular perfusion pressure to 30 mm Hg, these monkeys showed increased C-deoxyglucose uptake in the optic nerve head, suggesting increased anaerobic glycolysis.66 In humans, preliminary evidence suggests that aging fails to alter basal perfusion of the optic nerve head,18 but the effect of aging on the breadth of the autoregulatory range has not been investigated.

**Metabolic Autoregulation**

Animal studies using the laser Doppler flowmeter and flickering light find that optic nerve head perfusion rises 2- to 3-fold over steady light conditions.66-68 Concentrations of K⁺ in the vitreous immediately adjacent to the optic nerve head, an indirect measure of neuronal activity, closely track the blood flow changes.66 and comparison with electrophysiological responses suggests that blood flow rises in proportion to rising ganglion cell activity.65 Inhibitions of nitric oxide synthase blocks the blood flow rise.68

In cats, flickering light that augments retinal perfusion by 40% (microsphere method) increases optic nerve head blood flow by more than 250%.24 It is possible that, for the anterior nerve, these data reflect both a greater capacity for vasodilation and a greater risk for ischemia, under conditions of increased metabolic demand.23 Human studies of optic nerve perfusion under conditions of increased metabolic demand have not been performed. Patients with glaucoma exhibit decreased optic nerve head perfusion69 and higher levels of 3 isoforms of nitric oxide synthase locally,70 suggesting that excessive amounts of nitric oxide, perhaps synthesized in response to blood flow deficiency, may in turn be neurodestructive in this illness.70

Table 1. Regulation of the Retinal Circulation

<table>
<thead>
<tr>
<th>Pressure autoregulation</th>
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<tr>
<td>Does aging affect set point or upper and lower limits of range?</td>
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<tr>
<td>Does atherosclerosis increase risk of ischemia when perfusion pressure decreases?</td>
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<tr>
<td>Individual variation in breadth of range?</td>
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<td>Elevation in intracocular pressure vs reduction in mean arterial pressure: identical?</td>
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<tr>
<th>Metabolic autoregulation</th>
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<tr>
<td>Do increases in flow match increases in metabolism?</td>
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<tr>
<td>Do aging or atherosclerosis reduce vasodilatory capacity?</td>
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<tr>
<td>Mechanism of action of acute and chronic hyperglycemia?</td>
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<tr>
<td>Responses to oxygen and carbon dioxide</td>
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<tr>
<td>Is choroidal hyperoxic vasoconstriction absent at birth?</td>
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<td>Can carbon dioxide reactivity predict disease risk?</td>
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Responses to Oxygen and Carbon Dioxide

As in the retina and whole brain, increasing and decreasing arterial oxygen content fosters reciprocal changes in perfusion within the optic nerve head.11,12 Further, increased arterial PCO₂ increases optic nerve head blood flow, apparently much as it does in the retinal and cerebral circulations.13 These and other studies using laser Doppler flowmetry or confocal scanning laser Doppler flowmetry require cautious interpretation, since at least one study argues that these methods only provide information from the superficial nerve fiber layer, such that the results pertain to the nerve fiber layer, superficial nerve fiber layer, and the outer plexiform layer.14

Table 2. Regulation of the Optic Nerve Circulation

<table>
<thead>
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<th>Pressure autoregulation</th>
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<tr>
<td>Altered by aging or atherosclerosis?</td>
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<tr>
<td>Similar in all regions of the disc?</td>
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<tr>
<td>Lacking in some individuals?</td>
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<td>Elevation in intracranial pressure vs reduction in mean arterial pressure: identical?</td>
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<table>
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<tr>
<th>Metabolic autoregulation</th>
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<tr>
<td>Very large flow increases during flicker stimulation?</td>
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<tr>
<td>Do aging or atherosclerosis reduce vasodilatory capacity?</td>
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<tr>
<td>Responses to oxygen and carbon dioxide</td>
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<tr>
<td>Vigorous in health: equally vigorous in disease?</td>
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Table 2 summarizes the important questions regarding regulation of optic nerve head perfusion.

COMMENT

Retinal and optic nerve head blood flow regulation mirrors cerebrovascular regulation: (1) pressure autoregulation maintains a constant flow over a wide range of perfusion pressures; (2) metabolic autoregulation allows the flow to match metabolic demands; (3) altering arterial oxygen content generates reciprocal flow changes, maintaining constant oxygen delivery; and (4) decreasing extracellular pH linearly elevates perfusion. These general statements, however, are oversimplifications, and critical aspects of retinal and optic nerve head blood flow control remain inadequately explored. These include, (1) aging and atherosclerosis, whose well-defined cerebrocortical effects, if replicated in the eye, could predictably lead to a pathologic condition; (2) IOP elevation and arterial pressure reduction, which may act synergistically as risk factors for reduced ocular perfusion; and (3) the possibility that individual variation in regulation (possibly linked to different vessel architecture17,18) could increase disease susceptibility. Exploitation of these and other issues regarding hemodynamic control in the eye will increase understanding of both disease mechanisms and potential routes to therapy.

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REFERENCES


Corresponding author: Alon Harris, PhD, Department of Ophthalmology, Indiana University School of Medicine, Indianapolis, IN 46202-6195.
A look at the past...

A native of the Long Island was complimented by me recently on the style of her dress, and the smart appearance it gave her, when, to my surprise and amusement, stepping forward and waving the point of her finger by putting it on her tongue, she placed the finger on my right eye, saying: “Fluch do shul eugal gum bi mi air no ghonad.” (“Wet your eye for fear that I may be wounded.”) She did this very good-naturedly, and explained that when one is the subject of what he may suspect to be envious praise, either in respect of person or clothing, he may protect himself from consequences that might result from the Evil Eye, by performing this ceremony on the one who has done the praising.