

Harris
Jonescu-Cuypers
Kagemann
Giulla
Krieglstein



Atlas of
**Ocular
Blood Flow**

Vascular Anatomy, Pathophysiology, and Metabolism



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Atlas of Ocular Blood Flow — *Vascular* *Anatomy, Pathophysiology, and* *Metabolism*

Alon Harris, MSc, PhD

Professor of Ophthalmology, Professor of Physiology and Biophysics, and holder of the Letzter Endowed Chair; Co-Director of Age-Related Macular Degeneration Clinical & Research Center; Director of Glaucoma Research and Diagnostic Center, Department of Ophthalmology; Indiana University School of Medicine, Indianapolis, Indiana.

Christian P. Jonescu-Cuypers, MD, PhD

Department of Ophthalmology, University Eye Hospital of Cologne, Cologne, Germany, Ophthalmologist and Head of Laboratory of Biomorphometry and Retinal Perfusion Analysis Cologne; Assistant Director Medical Imaging, Glaucoma Research and Diagnostic Center, Indiana University School of Medicine, Indianapolis, Indiana

Larry Kagemann, MS, BME

Biomedical Research Engineer and Assistant Director, Glaucoma Research and Diagnostics Center, Department of Ophthalmology, Indiana University School of Medicine, Indianapolis, Indiana

Thomas A. Ciulla, MD

Retina Specialist, Midwest Eye Institute, Indianapolis, Indiana

Günter K. Kriegelstein MD, PhD

Professor of Ophthalmology, Director and Chairman, Department of Ophthalmology, University Eye Hospital of Cologne, Cologne, Germany

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To

My precious children, Danielle and Jonathan,
who are truly my inspiration and continually fill
my life with love and joy.

Alon Harris



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Preface

Undoubtedly two of the most rapidly growing fields within ophthalmology are ocular blood flow and imaging technology. This atlas examines the vascular anatomy and physiology of the eye as well as the assessment of ocular circulation in health and disease. It offers a cutting-edge analysis of the eye's blood supply and how it is affected by conditions such as glaucoma, age-related macular degeneration, and diabetic retinopathy.

Section one reviews the vascular anatomy from the heart to the eye. Within the eye, the retinal and uveal circulation are presented with illustrations created especially for this atlas. Detailed structures are revealed, including extensive coverage of the complex vasculature which nourishes the optic nerve head. These drawings are supplemented with histological sections that provide unique insights into the vascular structures of the eye.

Section two presents conceptual basis and details of blood flow measurement technology. Beginning with the physical principles, this section systematically reviews instrumentation measuring various aspects of ophthalmic pulsatility, the various light and sound Doppler techniques, and analytical approaches in ophthalmic angiography. The scientific and clinical strengths and weaknesses of each technique are discussed.

Section three presents the role of ocular hemodynamics in a wide range of ocular pathologies. Various imaging technologies showcase the vascular aspects of a variety of ocular diseases, with particular emphasis on age-related macular degeneration, diabetic retinopathy, and glaucoma.

Section four summarizes some of the newly-developed technologies on the forefront of ocular blood flow assessment, including assessment of retinal metabolism. Quantification of retinal oxygen saturation by several means is presented, as well as new combinations of techniques for simultaneous acquisition of data.

This book is meant to convey scientific and clinical information succinctly through an atlas format supplemented with appropriate text. Information presented in this book is current at the time of printing; however this nascent field is undergoing rapid growth both conceptually and technologically. The editors hope that this book will contribute to this rapid growth through effective dissemination of information on perhaps the most exciting topic within ophthalmology.

The authors



Foreword

"When you can measure what you are speaking about, and express it in numbers, you know something about it; but when you cannot measure it, when you cannot express it in numbers, your knowledge is of a meager and unsatisfactory kind: it may be the beginning of knowledge, but you have scarcely, in your thoughts, advanced to the stage of science."

William Thomson, Lord Kelvin, 1824–1907

The investigation and understanding of ocular blood flow has undergone a dramatic evolution in the final decade of the twentieth century. Current techniques of non-invasive measurement of ocular blood flow have contributed significantly to the understanding of the role of ocular hemodynamics in a whole variety of ocular diseases. The pathogenesis of age-related macular degeneration, diabetic retinopathy and glaucoma, the three leading causes of blindness in the developed world, may be linked to altered ocular blood flow.

This book is written for clinicians and researchers. It brings together internationally renowned experts in clinical ophthalmology, physiology and biomedical engineering to create a current and comprehensive view on ocular blood flow. This unique book combines an atlas with text, to achieve a visually outstanding body of information on a crucially important and rapidly evolving field of ophthalmology. Each chapter is

authoritatively presented with highly informative figures combined with enlightening text. The book comprehensively and logically presents; vascular anatomy from the heart to the eye, the retinal and uveal circulation, blood flow imaging and measurement technology, the role of ocular hemodynamics in ocular disease, in addition to cutting edge technologies for ocular blood flow and oxygen saturation assessment.

We expect many of the techniques and concepts described to become part of clinical practice in the future. This illuminating book is an enormous contribution to our knowledge of the rapidly expanding and evolving field of ocular blood flow imaging and assessment.

Robert D. Yee, M.D., F.A.C.S.
Professor of Ophthalmology
Chair, Department of Ophthalmology
Indiana School of Medicine

Ocular Vascular Anatomy

Vasculature from the Heart to the Eye

The aortic artery carries oxygenated blood from the heart. The first two arteries branching from the aorta are the brachiocephalic artery, which supplies the right arm and right common carotid artery, and the left common carotid artery (Figure 1.1). Each common carotid artery branches into the internal and external carotid arteries. The blood supply to the orbit arises primarily from the ophthalmic artery (OA), which is the first branch of the internal carotid artery and the only branch of the internal carotid outside the cranium (Figure 1.2). Smaller vascular contributions come from the external carotid artery via the internal maxillary artery and the facial artery. The OA runs inferiorly to the optic nerve as it enters the orbit through the optic canal. The OA then runs superiorly to the optic nerve as it courses nasally and anteriorly. Its major branches include branches to the extraocular muscles, the central retinal artery, and the posterior ciliary arteries (Figure 1.3).

Several of the multiple branches of the OA—the supra-orbital, lateral and medial palpebral, and lacrimal arteries—communicate with the facial artery to form an

anastomosis between the internal and external carotid arteries.

The central retinal artery (CRA) branches off the OA to penetrate the optic nerve approximately 10 to 15 mm behind the globe (Figure 1.4). The CRA courses adjacent to the central retinal vein within the central portion of the optic nerve. It then emerges from the optic nerve within the globe, where it branches into four major vessels. The CRA supplies the inner two-thirds of the retina (Figure 1.5), the most anterior portion of the optic nerve head (the superficial nerve fiber layer), and to some extent the retrolaminar optic nerve.

A medial and a lateral posterior ciliary artery (PCA) branch from the OA. Occasionally an aberrant PCA is also present. Each medial and lateral PCA divides into one long posterior ciliary artery (LPCA) and seven to ten short posterior ciliary arteries (SPCAs) before piercing the sclera (Figure 1.6). The peripapillary and posterior choroid up to the equator is primarily supplied by the SPCAs, while the more anterior regions of the choroid are supplied by the LPCAs and the anterior ciliary arteries (Figure 1.7). The anterior ciliary arteries are derived from

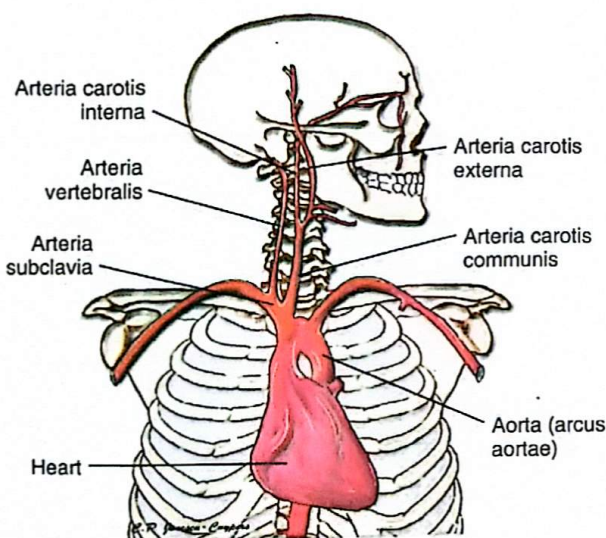


FIGURE 1.1

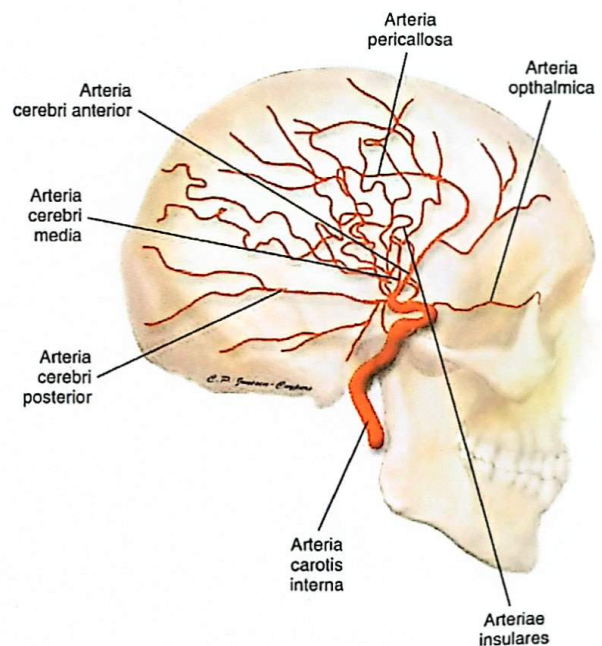


FIGURE 1.2

2 section 1 Ocular Vascular Anatomy

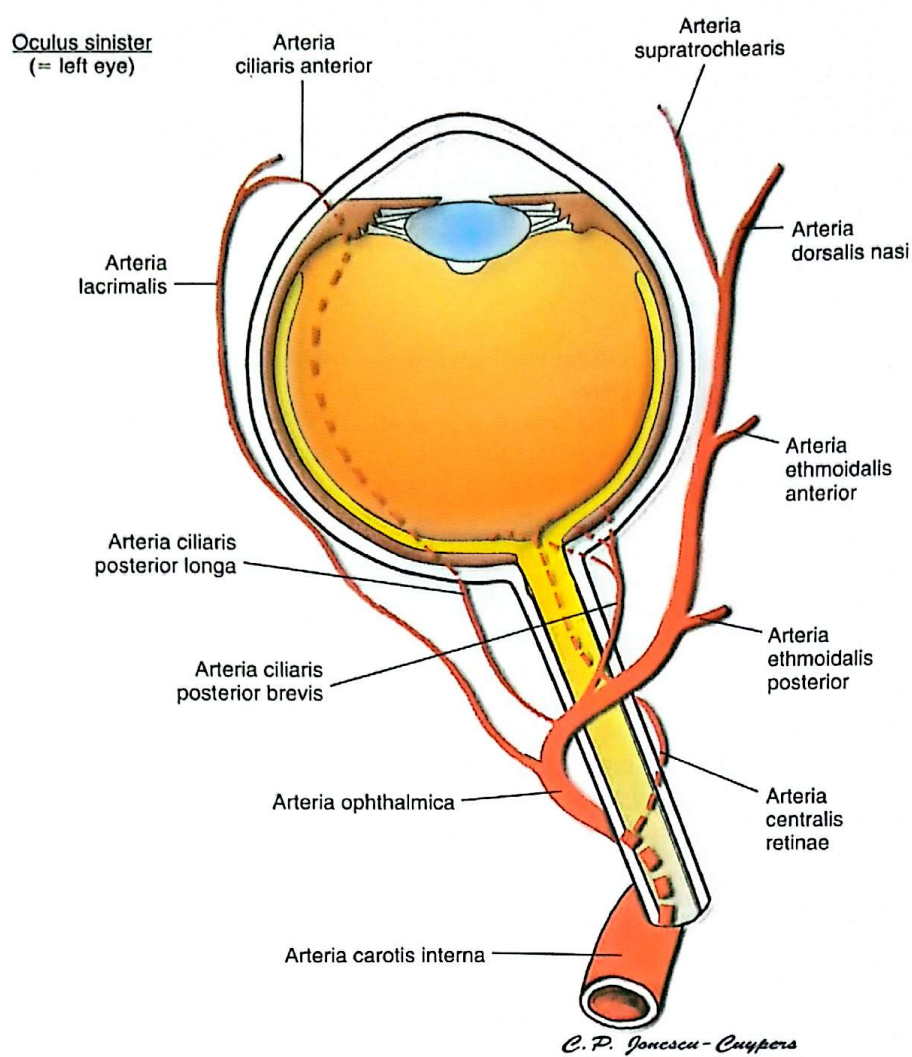


FIGURE 1.3

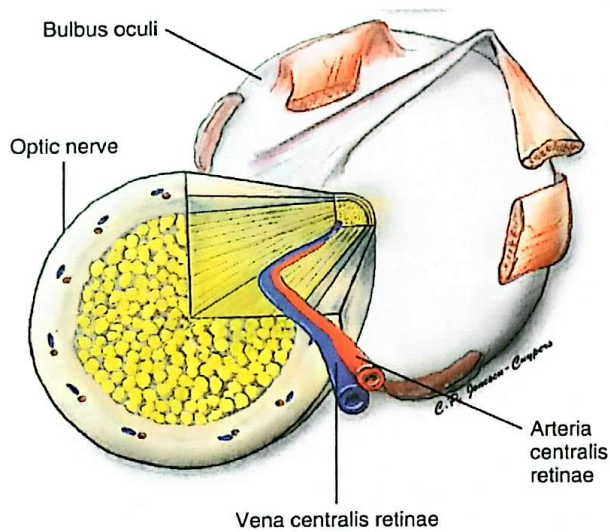


FIGURE 1.4

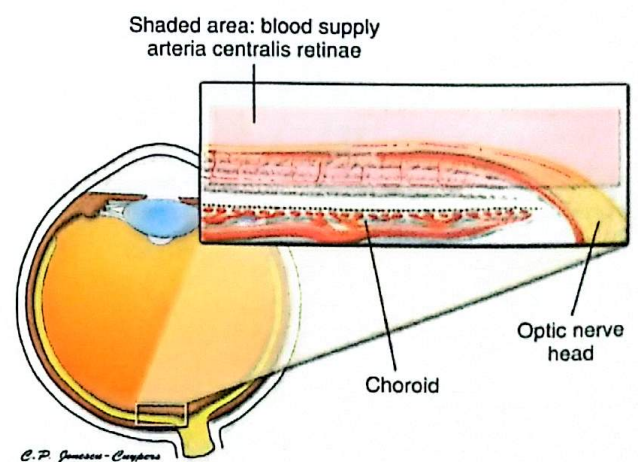


FIGURE 1.5

the muscular branches and carry the principal blood supply to the anterior segment of the eye, running to the front of the eyeball in company with the tendons of the recti muscles. Each rectus muscle is accompanied by two vessels (except the lateral rectus having usually only one). The vessels form a vascular zone beneath the conjunctiva, then piercing the sclera a short distance from the cornea ending in the *circulus arteriosus iridis major*.

Vasculature of the Retina

The nutritional and waste removal needs of the retina are met by two separate sources. The CRA supplies approxi-

mately the inner two-thirds of the retina (see Figure 1.5). The deeper outer layers, including photoreceptors and bipolar cells, are nourished by the uveal system, specifically the choriocapillaris. The retinal pigment epithelial layer, which separates the retina from the choroid, actively transports metabolites and waste to and from the deep layers of the retina to the choroid (Figure 1.8). The CRA typically branches into four major trunks, each of which supplies a quadrant of the retina (Figure 1.9). The retinal arteries and veins lie within the nerve fiber layer of the superficial retina. The retinal capillaries run parallel to the retinal nerve fiber layer (Figure 1.10). In the posterior pole, the retinal capillaries form several layers and are higher in number than in the more peripheral retina. The

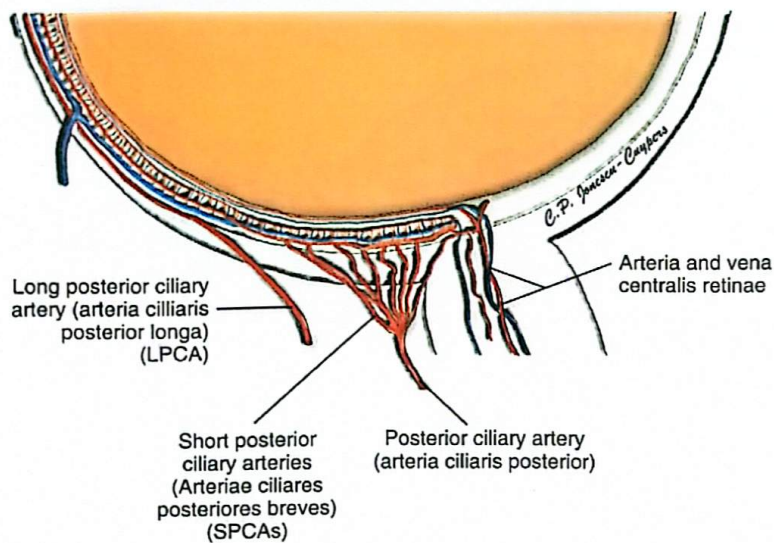


FIGURE 1.6

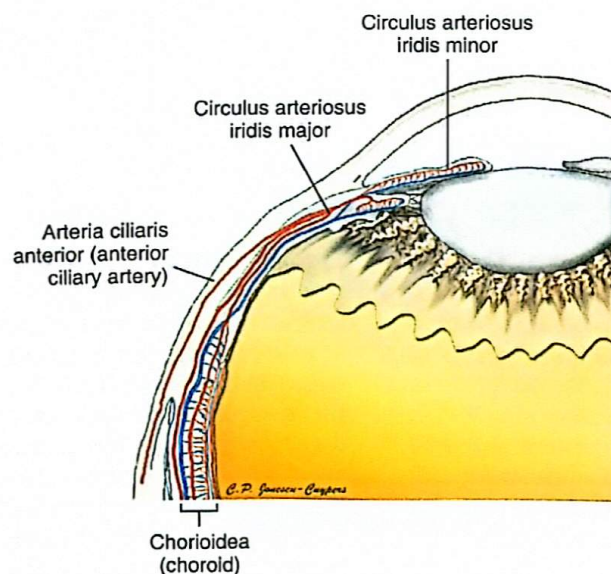


FIGURE 1.7

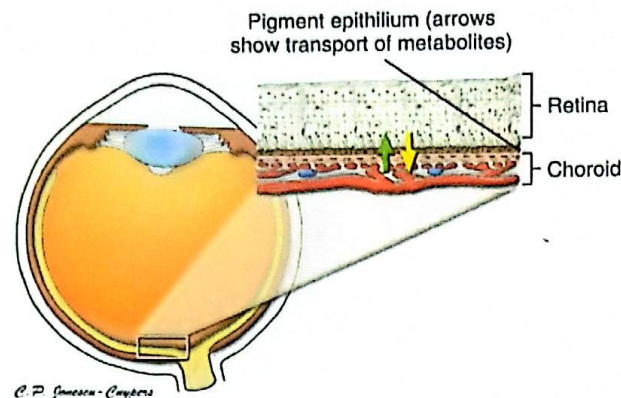


FIGURE 1.8

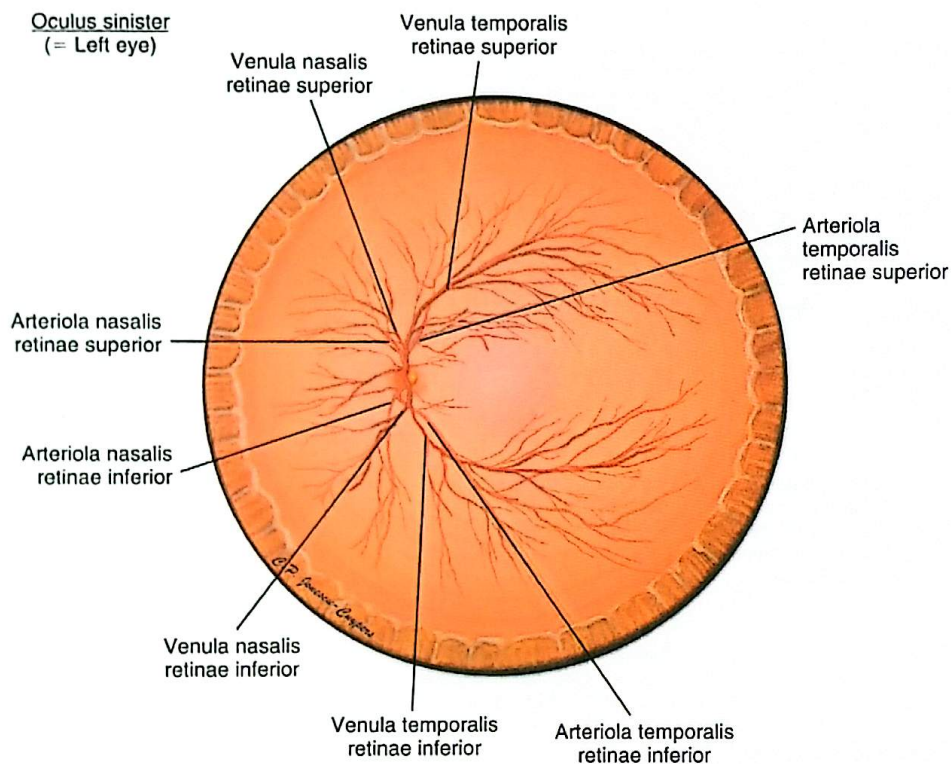


FIGURE 1.9

peripapillary retina often has a superficial layer of fine capillaries. In approximately 30% of all people, a cilio-retinal artery may be present and supply a variably sized region of the retina, temporal to the optic nerve (see Figure 3.87). The cilio-retinal artery, if present, may be a direct branch of the ciliary or choroidal arteries and emerges from the temporal aspect of the optic nerve, extending laterally along the papillomacular bundle.

Retinal venous drainage occurs via the central retinal vein, which exits the eye through the optic nerve and parallels the CRA (Figure 1.11). The central retinal vein drains into the superior ophthalmic vein or, rarely, directly into the cavernous sinus.

Vasculature of the Anterior Optic Nerve

Despite extensive research, the precise microvascular anatomy of the anterior optic nerve and peripapillary region remains difficult to ascertain. Small vessel caliber, the complex three-dimensional angioarchitecture, and the relative inaccessibility of the tissue all make it difficult to study the vasculature of the optic nerve head.

The anterior optic nerve is divided into four anatomic regions (Figure 1.12). The only region visible by fundus exam, the superficial nerve fiber layer, is continuous with

Oculus dexter
(= Right eye)

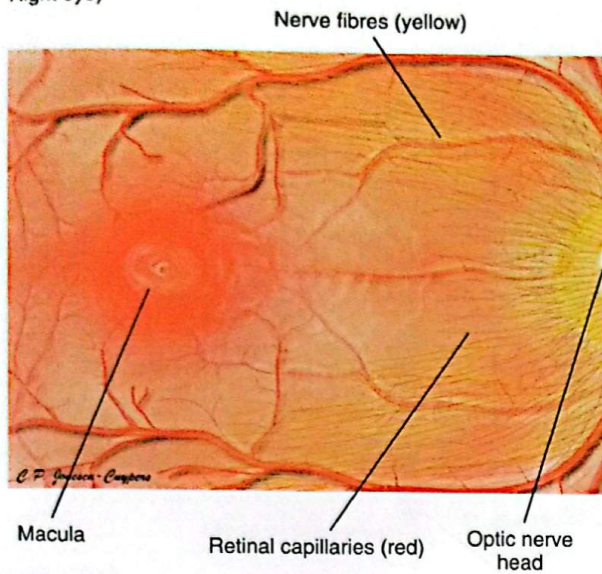


FIGURE 1.10

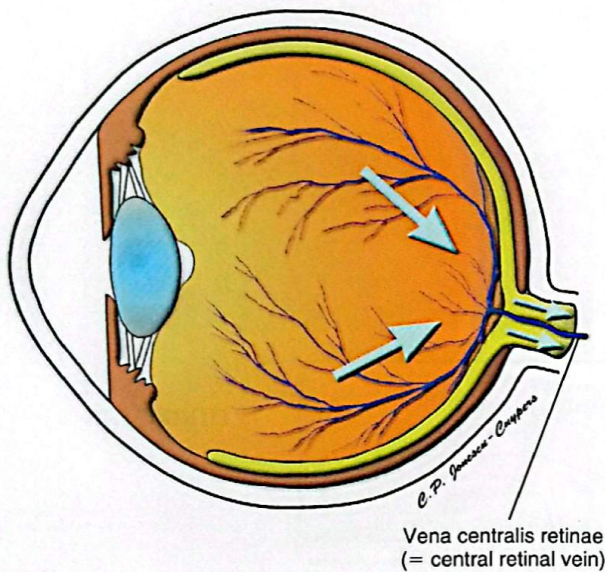


FIGURE 1.11

the nerve fiber layer of the retina (Figure 1.12, *yellow shaded*). Immediately posterior to the nerve fiber layer is the prelaminar region, which lies adjacent to the peripapillary choroids (Figure 1.12, *red shaded*). Posterior to the prelaminar region, the lamina region is continuous with the sclera and is composed of the lamina cribrosa—a structure consisting of fenestrated connective tissue lamellae, which allow neural fibers to pass through the scleral coat (Figure 1.12, *green shaded*). Finally, the retrolaminar region lies posterior to the lamina cribrosa, marked by the beginning of axonal myelination, and is

surrounded by the meninges of the central nervous system (Figure 1.12, *blue shaded*).

The superficial nerve fiber layer receives blood from recurrent retinal arterioles arising from the branches of retinal arteries (Figure 1.13). These small vessels (called "epipapillary vessels"), originating in the peripapillary nerve fiber layer, run toward the center of the optic nerve head. The temporal nerve fiber layer may have an arterial supply from the cilioretinal artery when it is present. No direct choroidal or choriocapillaris contribution is observed in this region.

The prelaminar region is mainly supplied by direct branches of the short PCAs and by branches of the circle of Haller and Zinn (Figure 1.14; see also Figures 1.12 and 1.15). The circle of Haller and Zinn is a complete or incomplete arterial ring of arterioles that often exists within the perineural sclera (Figure 1.15). This structure is formed by the confluence of branches of the short PCAs. The arterial circle provides multiple perforating branches into the prelaminar region, lamina cribrosa, and retrolaminar pial system, to the peripapillary choroid, and to the pial arterial system. Arterial branches emerge from the circle of Haller and Zinn to supply both the prelaminar and lamina regions. The direct arterial supply to the prelaminar region arising from the choroidal vasculature is minimal. Several small centripetal arteries or arterioles branch from the larger vessels of the peripapillary choroid, but no direct connection between the peripapillary choriocapillaris and the prelaminar region exists.

The lamina cribrosa region also receives its blood supply from branches of the short PCAs or from branches of the circle of Haller and Zinn. These precapillary branches perforate the outer aspects of the lamina cribrosa before branching into an intraseptal capillary network. As in the prelaminar region, the larger vessels of the peripapillary choroid may contribute occasional small arterioles to the lamina cribrosa region (see Figure 1.15).

The retrolaminar region has two blood supplies: the CRA and the pial system. The pial system is an anastomosing network of capillaries located immediately within the pia mater. The pial system originates at the circle of Haller and Zinn and may also be fed directly by the short PCAs. The branches of the pial system extend centripetally to nourish the axons of the optic nerve (Figure 1.16). The CRA may supply several small intraneural branches in the retrolaminar region. Some of these branches may anastomose with the pial system.

The venous drainage of the anterior optic nerve is almost exclusively via the central retinal vein (see Figure 1.11). In the nerve fiber layer, blood is drained directly into the retinal veins, which then join to form the central retinal vein. In the prelaminar, lamina, and retrolaminar regions, venous drainage also occurs via the central retinal vein or axial tributaries to the central retinal vein.

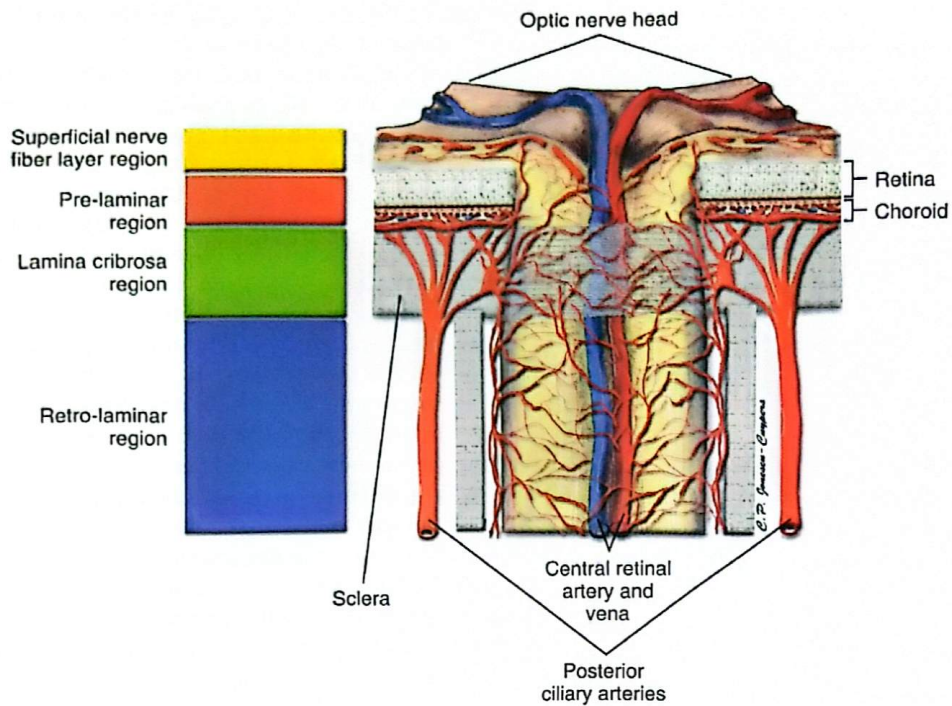


FIGURE 1.12

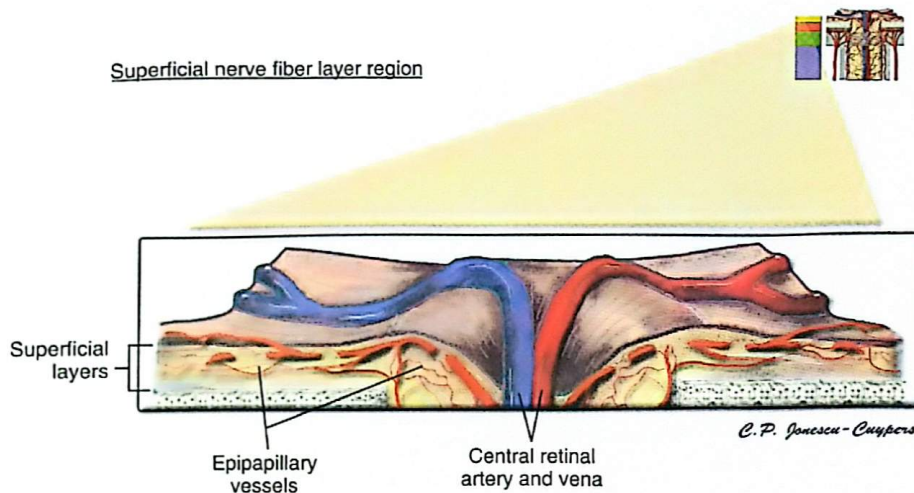


FIGURE 1.13

Vasculature of the Choroid

The outer choroid is composed of large nonfenestrated vessels, whereas the inner choroid has a much smaller vessel caliber. The innermost layer of the choroid, the choriocapillaris, is composed of richly anastomotic, fenestrated capillaries beginning at the optic disc margin (Figure 1.17). The capillaries of the choriocapillaris are separate and distinct from the capillary beds of the anterior optic nerve.

The SPCAs supply most of the optic nerve head and the portion of the choriocapillaris posterior to the equator. The choriocapillaris anterior to the equator is supplied by the LPCAs and the anterior ciliary arteries (ACAs). The LPCAs pierce the sclera and course anteriorly through the suprachoroidal space to branch near the ora serrata. Each LPCA then sends three to five branches posteriorly to supply the choriocapillaris anterior to the equator. The ACAs, branches of the OA, accompany the rectus muscles anteriorly to supply the major circles of

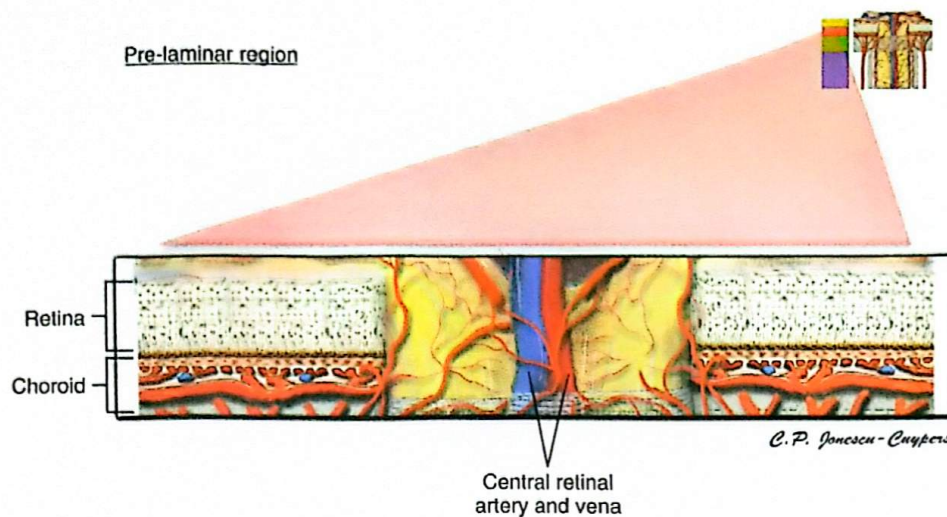


FIGURE 1.14

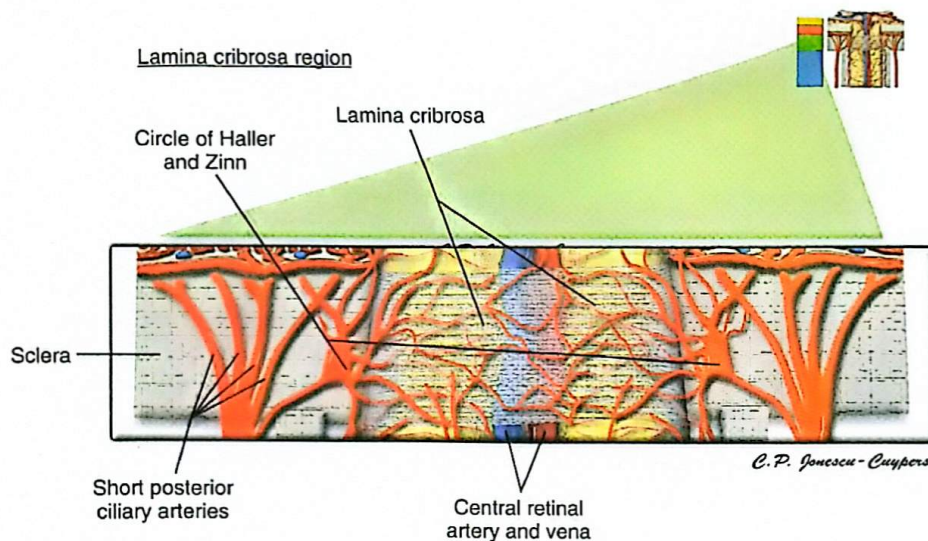


FIGURE 1.15

the iris (Figure 1.18). Before reaching the iris, 8 to 12 branches pass posteriorly through the ciliary muscle to supply the anterior choriocapillaris together with the LPCAs (see Figure 1.6). Functional anastomoses between the choriocapillaris anterior and posterior to the equator have not been demonstrated. This represents a peripheral choroidal watershed zone.

Venous drainage from the choriocapillaris is mainly through the vortex veins. Minor drainage occurs through the ciliary body via the anterior ciliary veins. The vortex veins drain into the inferior ophthalmic vein (IOV) and superior ophthalmic vein (SOV) (Figure 1.19). The SOV exits the orbit through the superior orbital fissure and drains into the cavernous sinus. The IOV sends a branch to the SOV and then exits the orbit through the inferior orbital fissure into the pterygoid plexus.

Variability of Vascular Patterns

Marked variation is observed in the vascular patterns of the anterior optic nerve, peripapillary retina, and the posterior choroid among individuals. The predominant difference is in the arterial supply. Varying numbers of branches have been found in the PCAs, the SPCAs, the number of branches from the LPCAs, and the number of branches from the ACAs.

ANATOMIC VARIATIONS

Ophthalmic Artery

The OA usually passes over the optic nerve but can pass below the optic nerve as it continues in the orbit medial to the optic nerve.

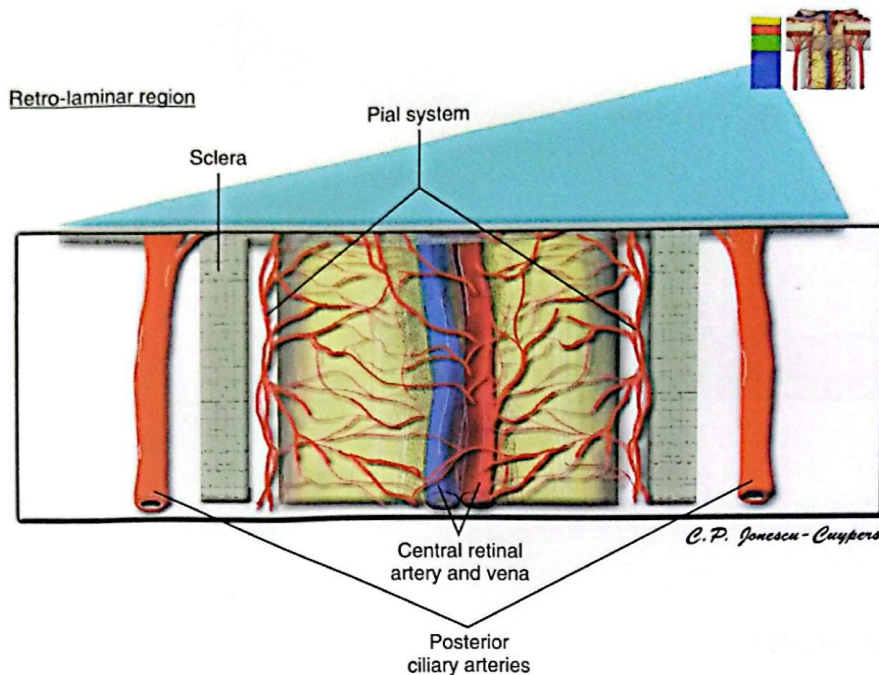


FIGURE 1.16

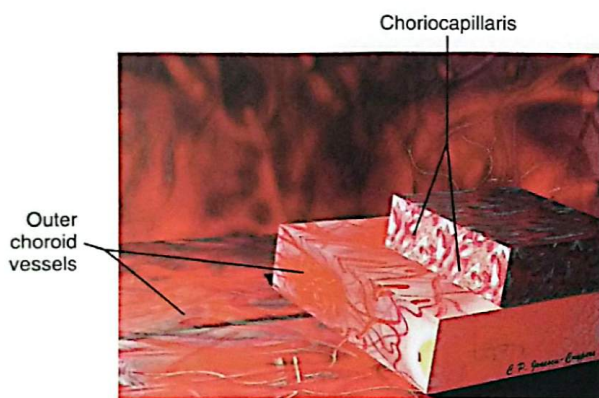


FIGURE 1.17

Ciliary Arteries

Usually one main ciliary artery arises from the first segment of the OA and supplies the choroid of the nasal hemisphere, and usually one main ciliary artery arises from the second segment of the OA and supplies the temporal choroid. More than 5 main ciliary arteries can branch into 20 SPCAs and 2 LPCAs.

Cilioretinal Artery

Cilioretinal arteries typically appear ophthalmoscopically to arise from the temporal portion of the optic nerve head and to course along the maculopapillary bundle (see Figure 3.86). On fluorescein angiography, this artery will fill in the choroidal phase, before filling the CRA.

Vortex Veins

There are usually four to six vortex veins, which drain the choroidal circulation in a complex and variable fashion. For example, anastomotic vessels between vortex vein drainage areas have been identified in studies in which colored neoprene injected into a vortex vein exited immediately from the other vortex veins (see Figure 1.19).

Coloboma

Coloboma results from failure of the embryonic fissure to close along the inferior-nasal portion of the optic cup during development. This fissure typically closes at 33 to 40 days after conception. With incomplete closure posteriorly, both optic nerve head and choroidal coloboma can result. The entire optic nerve head can be involved in a colobomatous lesion. A choroidal coloboma typically presents as bare sclera on ophthalmoscopy (Figure 1.20).

Innervation and Retinal Circulation

Normally, retinal blood flow remains relatively constant over a substantial range of intraocular pressure and systemic blood pressure. Compared with the choroidal circulation (a high-flow, variable-rate system), the retinal circulation is a lower flow, constant-rate system supplying a highly metabolically active tissue. The choroid receives 85% of ocular circulation, as compared to 15% to the retinal circulation. The autonomic nervous system controls vascular resistance in the choroid. Sympathetic nerves provide most of the regulation through the cranial cervical

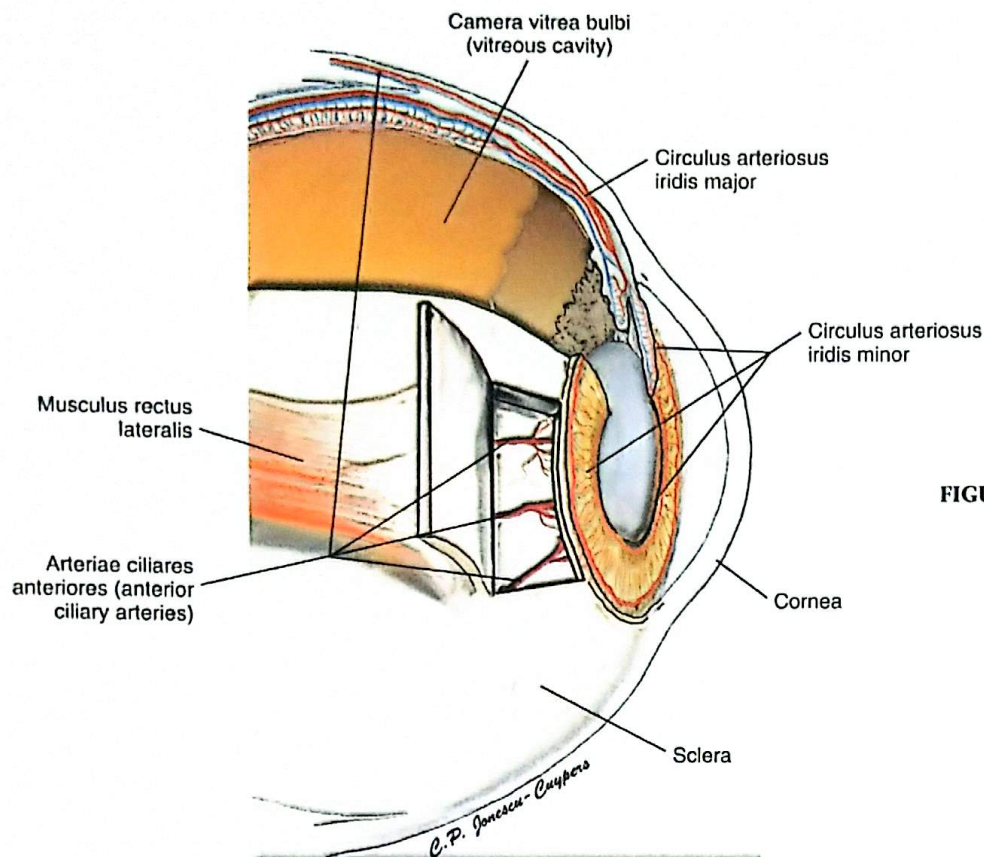


FIGURE 1.18

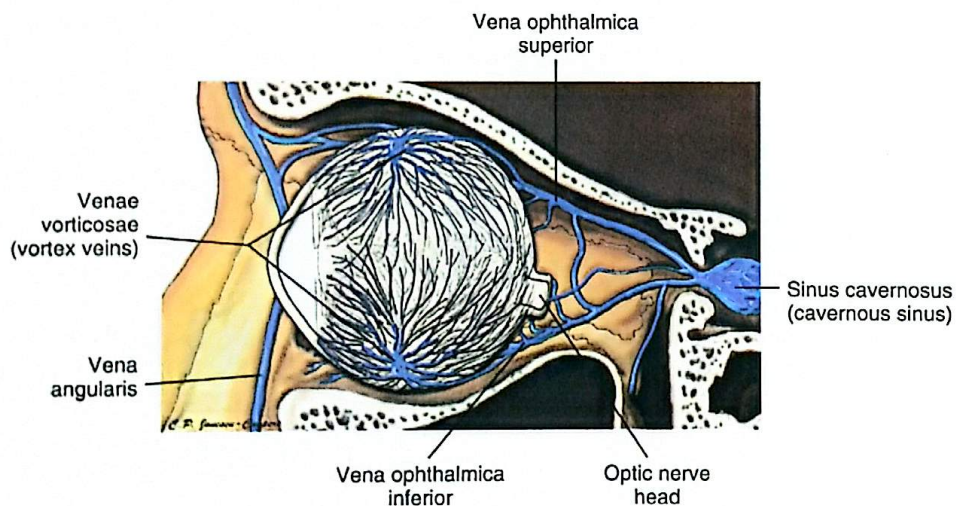


FIGURE 1.19

ganglion, involving neuropeptide Y and provoking vasoconstriction when stimulated. The parasympathetic system mediates poorly defined control. Choroidal blood flow shows modest autoregulation during perfusion pressure changes.

The autonomic nervous system contributes to retrobulbar and choroidal circulatory regulation, but it ends at

the lamina cribrosa, so the retinal and anterior optic nerve head (ONH) vasculature do not possess direct innervation. Although retinal and optic nerve head vessels have alpha-adrenergic, beta-adrenergic, and cholinergic receptors, the role of these receptors in vascular control remains unclear. Consequently, retinal blood flow is autoregulated locally in response to variable blood oxygen content, with



FIGURE 1.20

capillary recruitment and derecruitment presumably providing constant oxygen delivery.

Local Factors Affecting Vascular Tone

Several soluble vasoactive molecules mediate retinal vascular autoregulation, including endothelial-derived nitric oxide, endothelins, superoxide anions, renin-angiotensin, and vascular endothelial growth factor (VEGF). Nitric oxide is produced by two endothelial enzymes, constitutive nitric oxide synthase (membrane bound) and inducible nitric oxide synthase (cytosolic), both of which oxidize L-arginine to produce nitric oxide. Endothelial cell nitric oxide diffuses to the pericyte or smooth muscle cell surface, where it binds to guanylate cyclase, causing intracellular cGMP accumulation and vasodilation. Nitric oxide production is directly stimulated by increased local shear force, bradykinins, insulin-like growth factor 1, acetylcholine, thrombin, and various platelet products. In addition to its vasodilatory actions, nitric oxide protects vessels by inhibiting platelet aggregation, platelet granule secretion, leukocyte adhesion, and possibly smooth muscle cell proliferation.

Endothelins, another group of vasoactive molecules, are released by endothelial cells and bind to receptors on adjacent pericytes and smooth muscle cells. Endothelins (ET-1, ET-2, and ET-3, each with 21 amino acids) are the most potent vasoconstrictor agents currently known. Endothelin-dependent contraction is mediated by three receptor subtypes (ETR-A, ETR-B, and ETR-C). Human

studies show that vasoconstriction following intravenous injection of ET-1 is mediated through ETR-A. Several in vitro studies, using tissues from a variety of species, demonstrate that endothelins are involved in retinal microvascular control, and animal experiments substantiate in vitro findings that ocular blood flow can be profoundly influenced by endothelin activity. For instance, intravitreal injection of synthetic ET-1 into the cat eye causes retinal vasoconstriction and decreased ocular blood flow, with no change in iris, ciliary, or choroidal blood flow. In addition, hyperoxic retinal vasoconstriction in rats is apparently ET-1 dependent.

In addition to nitric oxide and endothelins, superoxide anions play a role in retinal microvascular autoregulation. Superoxide anions inactivate nitric oxide, thereby inhibiting vasodilatory capacity. The vascular endothelium generates basal levels of superoxide anions and can be stimulated to produce deleterious amounts of these molecules during many pathologic conditions. This pathologic inhibition may mediate vascular changes found in hypertension, hypercholesterolemia, retinopathy of prematurity, diabetes, and ischemia/reperfusion injury.

Another component of the retinal microvascular autoregulatory system is the renin-angiotensin pathway. Angiotensin-converting enzyme (ACE) on the luminal endothelial cell surface rapidly converts angiotensin I to angiotensin II, and ACE inactivates bradykinin. Angiotensin II stimulates retinal vasoconstriction via smooth muscle cells and pericytes. Isolated porcine ophthalmic arteries vasoconstrict in response to angiotensin II and relax in response to bradykinin via a nitric oxide-dependent mechanism. ACE-inhibitors used in this model prevent angiotensin-mediated constriction and potentiate bradykinin relaxation. After intravenous infusion of angiotensin II inhibitor, cerebral and ocular blood flow was examined in healthy subjects by Doppler sonography and fundus pulsation amplitudes and demonstrated little decrease in choroidal or optic nerve head blood flow. Angiotensin II decreased the resistive index and fundus pulsation amplitude and increased the mean flow velocities in both the ophthalmic and the middle cerebral arteries; however, when compared with systemically measured parameters of mean arterial pressure, the intraocular vessels were relatively insensitive to angiotensin II.

Exemplary Histologic Descriptions

The following histologic images demonstrate various aspects of normal and pathologic vasculature of the eye.

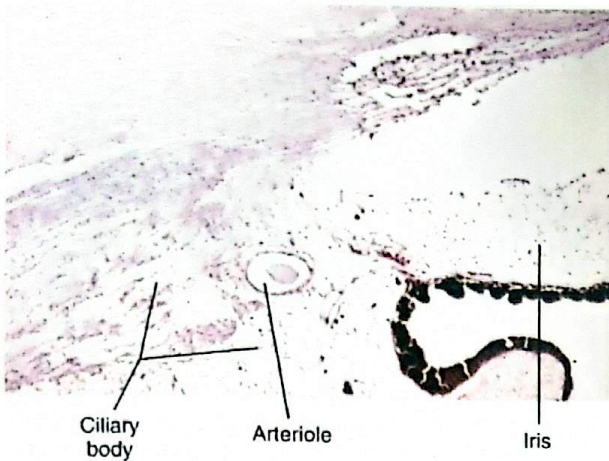


FIGURE 1.21 Anterior chamber angle with sclera (*top left*), ciliary body (*left*), and iris (*right*). A prominent large vessel is present at the root of the iris. This vessel belongs to the major arterioles supplying the iris and chamber angle with blood (periodic acid-Schiff [PAS] stain, original magnification $\times 25$).

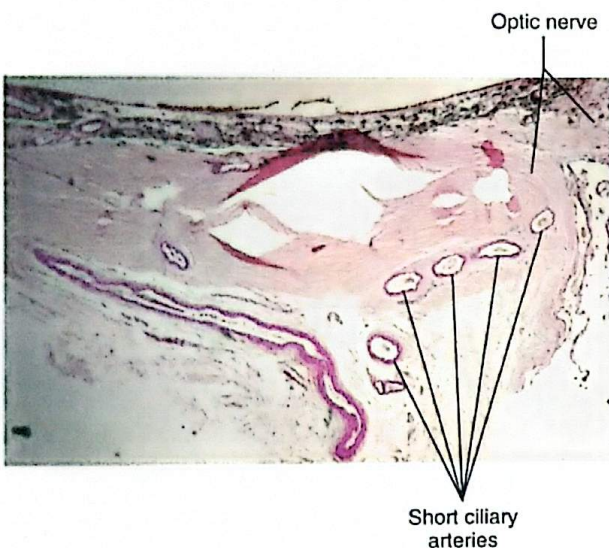


FIGURE 1.22 Section displaying the posterior sclera, optic nerve (*right*) and choroid showing sections of the short ciliary arteries posterior to the sclera (hematoxylin-eosin [HE] stain, original magnification $\times 10$).

FIGURE 1.25 Same aspect as in Figure 1.24 seen in lower power. The nerve protrudes completely through the sclera (PAS stain, original magnification $\times 10$).

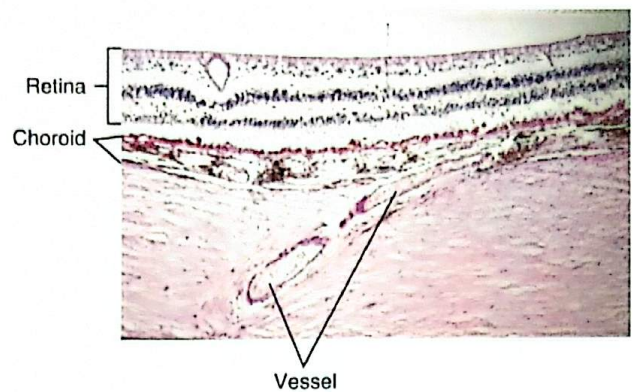


FIGURE 1.23 Close-up of a scleral canal with continuation of a vessel into the choroid (PAS stain, original magnification $\times 25$).

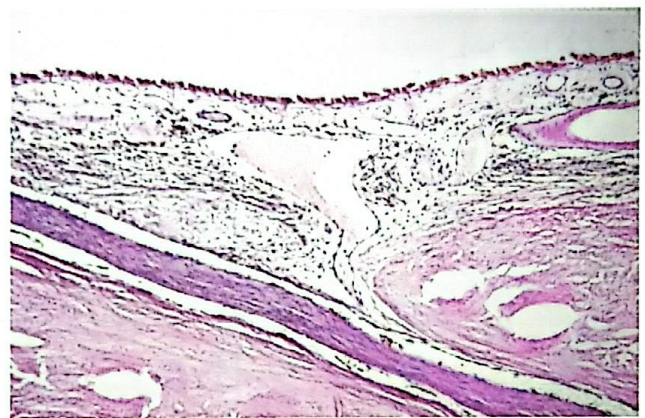
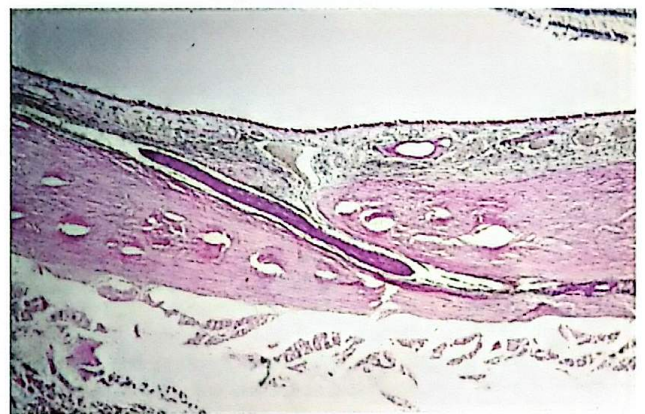


FIGURE 1.24 Another scleral canal entering the choroid. A prominent nerve is present with a large vessel (*center*). The retina is artifactually detached (PAS stain, original magnification $\times 25$).



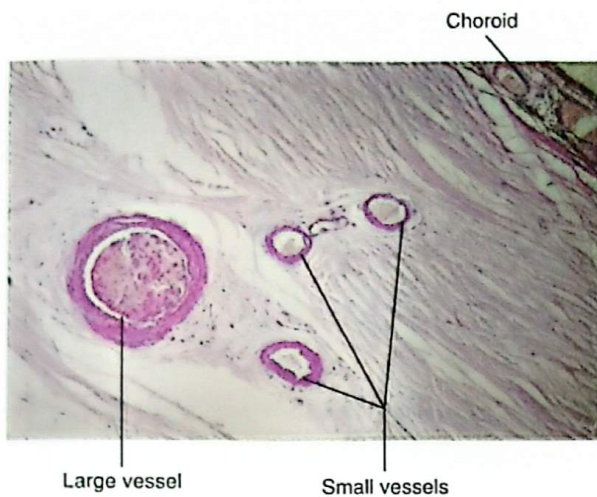


FIGURE 1.26 Scleral canal close to the posterior pole of the globe. A large and three smaller arteries are protruding through the sclera from the outer to the inner surface along a scleral canal. *Top right*, the choroid (PAS stain, original magnification $\times 25$).

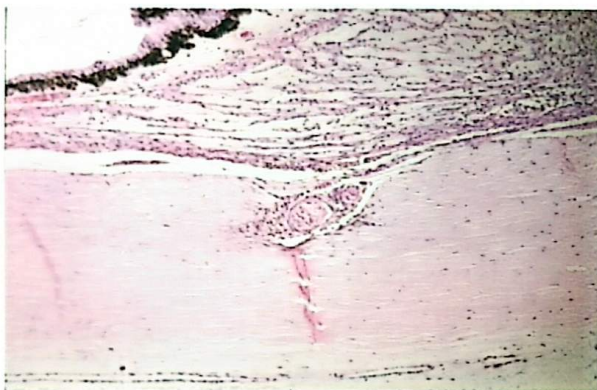


FIGURE 1.27 Scleral canal located more anteriorly supplying the ciliary body with vessels (HE stain, original magnification $\times 25$).

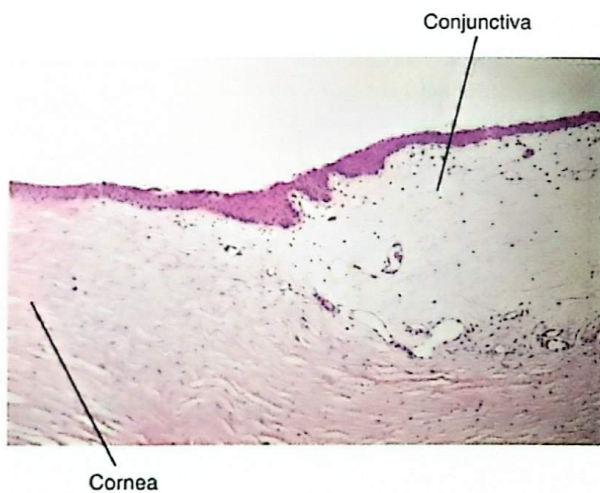


FIGURE 1.28 Limbal area with conjunctiva to the right and cornea to the left. Larger episcleral vessels are present in addition to smaller vessels located more superficially (HE stain, original magnification $\times 25$).

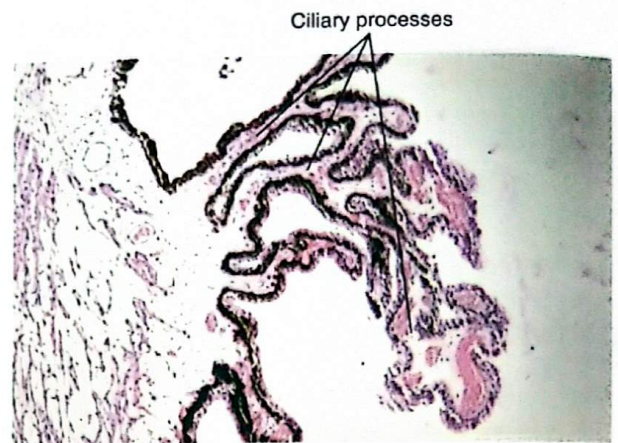


FIGURE 1.29 Ciliary processes showing an abundance of capillaries, which supply the ciliary epithelium (HE stain, original magnification $\times 25$).

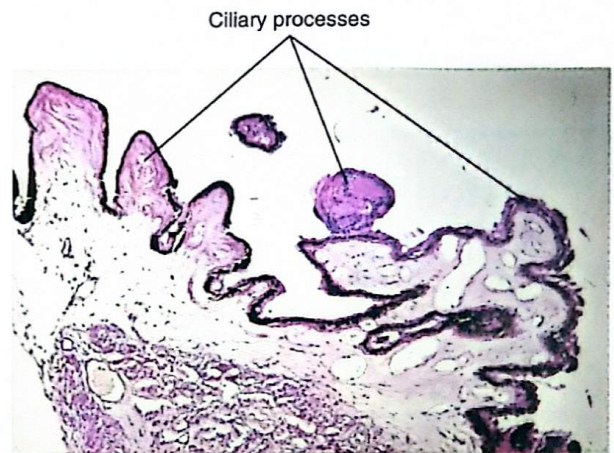


FIGURE 1.30 Ciliary processes with several dilated capillaries present. In addition, a Fuchs' adenoma is seen (PAS stain, original magnification $\times 25$).

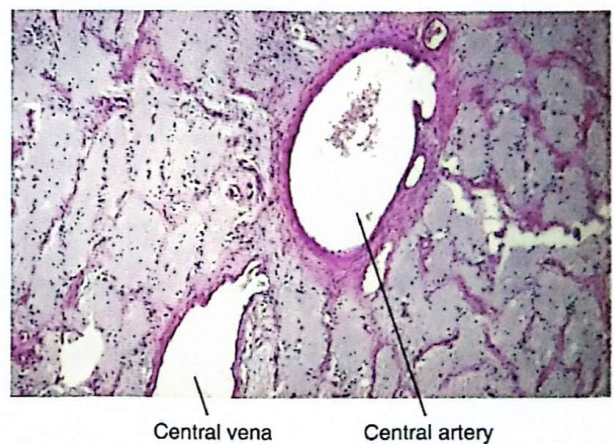


FIGURE 1.31 Cross section of the optic nerve. *Top*, central artery, and *below*, central vein (PAS stain, original magnification $\times 25$).

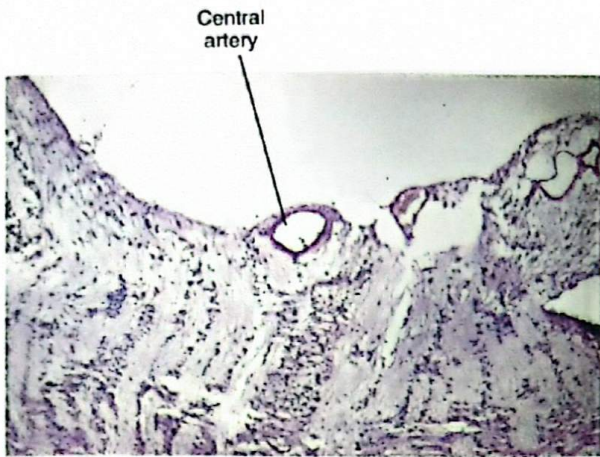


FIGURE 1.32 Longitudinal section of the optic nerve and central section of the optic nerve head with a prominent artery present in the center. Right off center is the vein (PAS stain, original magnification $\times 25$).



FIGURE 1.33 High-power view of large vessels (artery and vein) at the optic nerve head (HE stain, original magnification $\times 50$).

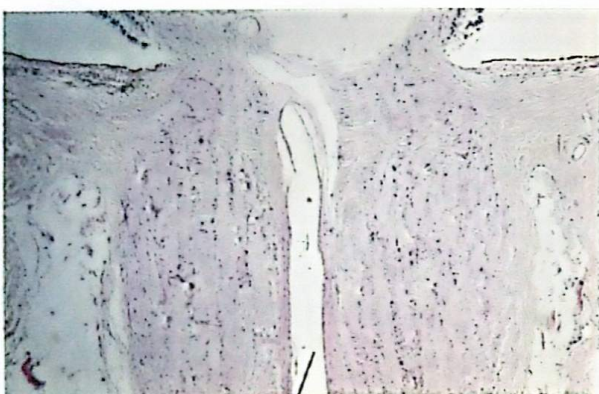


FIGURE 1.34 Longitudinal section of the optic nerve with a prominent central vein (HE stain, original magnification $\times 10$).



FIGURE 1.35 Longitudinal section of the optic nerve head with an artery and vein in a patient with diabetes (PAS stain, original magnification $\times 25$).

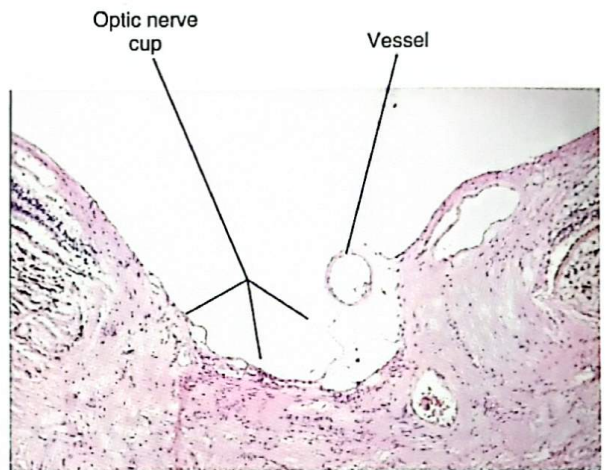


FIGURE 1.36 Optic nerve head of a patient with advanced glaucoma. The vessels are located in the area of the cup with loss of surrounding tissue (HE stain, original magnification $\times 25$).

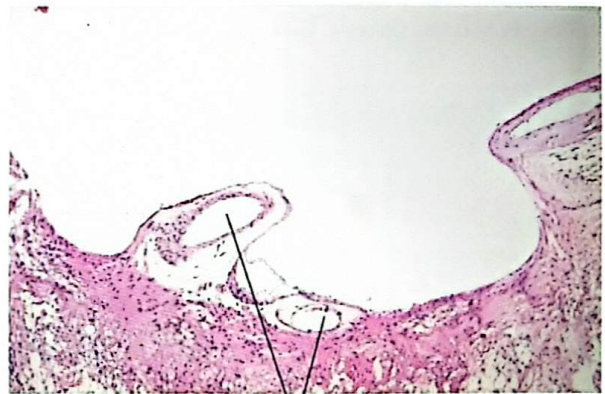
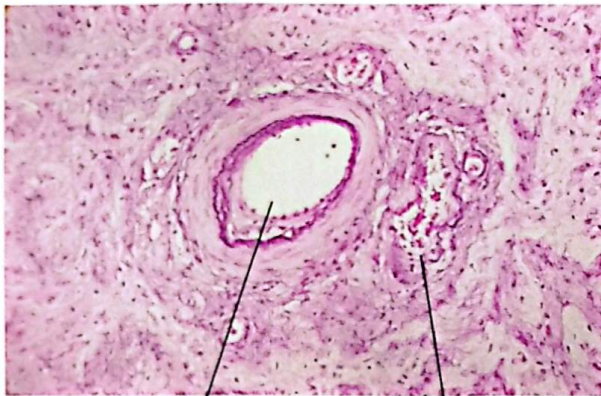


FIGURE 1.37 Glaucomatous cupping of the optic nerve head with vessels located in the cup and loss of the surrounding neural tissue (HE stain, original magnification $\times 25$).



FIGURE 1.38 Similar aspect as in Figure 1.37 showing in addition the centrally located large vessels in the optic nerve (PAS stain, original magnification $\times 10$).



Artery

Vena

FIGURE 1.39 Cross section of the optic nerve near lamina cribrosa. The strong muscular artery compresses the neighboring vena. Both are surrounded by a common adventitia. The venous lumen contains a partly recanalized thrombus (elastica stain, $\times 50$). (Courtesy B. Kirchhof, Cologne, Germany.)

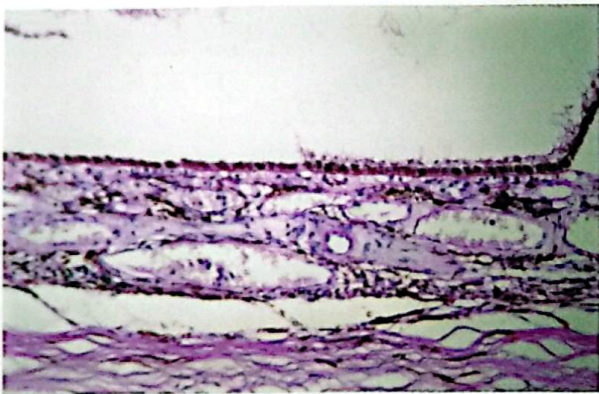
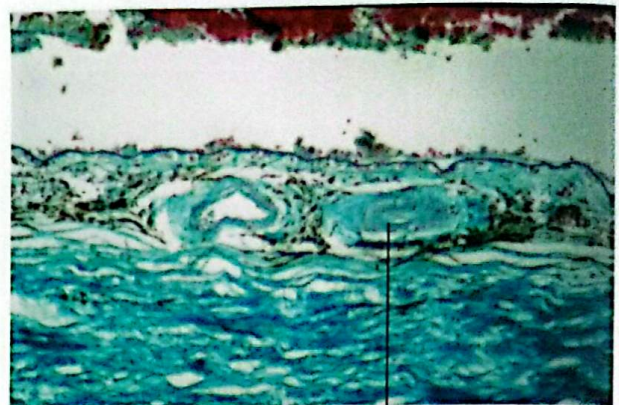
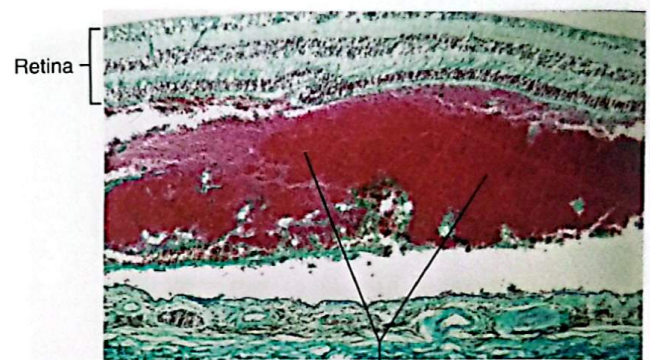


FIGURE 1.40 Normal choroidal vasculature with retinal pigment epithelium (RPE) and Bruch's membrane. Below, the capillaries are present. The retina is artifactually detached (PAS stain, original magnification $\times 50$).



Occluded vessel

FIGURE 1.41 High-power view of the choroid with an occluded larger vessel to the right of a vessel with a thickened wall (AZAN stain, original magnification $\times 50$).



Subretinal hemorrhage

FIGURE 1.42 Large subretinal hemorrhage evolving from a choroidal neovascular membrane. An artifactual gap is present between the outer portion of the choroidal neovascularisation (CNV) and the largely destroyed RPE (AZAN stain, original magnification $\times 25$).

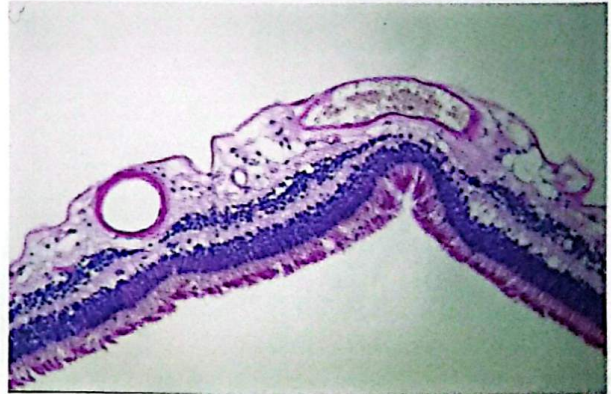


FIGURE 1.43 From bottom to top: The sclera, the choroid, and Bruch's membrane are present. Above Bruch's membrane is a choroidal neovascular membrane with several small capillaries, which originate from the choroid (PAS stain, original magnification $\times 25$).



FIGURE 1.44 Vasculature of the retina: A larger vessel to the right and small capillaries in both the inner and outer nuclear layers of the retina. *To the left*, a hypocellular epiretinal membrane is present (PAS stain, original magnification $\times 50$).



FIGURE 1.45 Regular pattern of larger vessels of the retina with an arteriole to the left and venules to the right (PAS stain, original magnification $\times 25$).

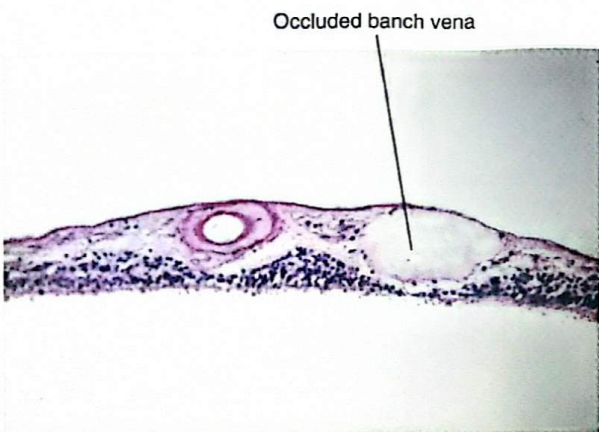


FIGURE 1.46 Aspect of retina with a branch vein occlusion. Note that the retina is thinner to the right compared with the left (PAS stain, original magnification $\times 50$).

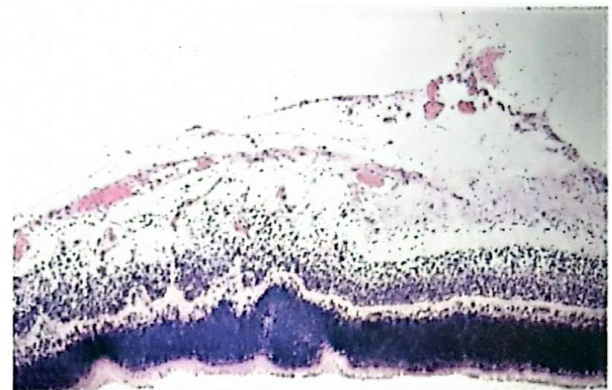


FIGURE 1.47 Cross section of the retina from an eye with retinopathy of prematurity (ROP). Epiretinal fibrocellular proliferations with newly formed blood vessels are present (H-E stain, original magnification $\times 25$).

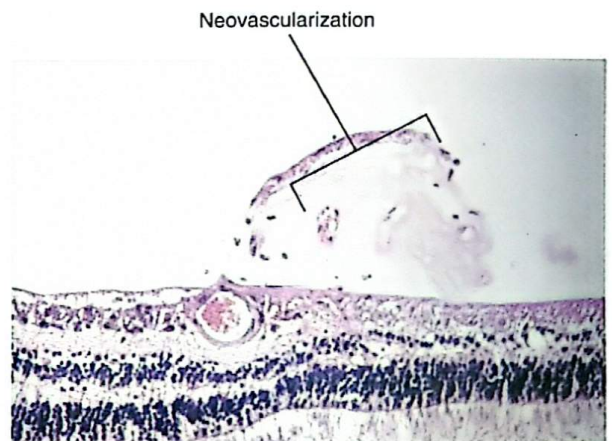


FIGURE 1.48 Cross section of the retina in a patient with diabetes. A neovascularization is protruding into the vitreous cavity arising from the retinal vasculature (H-E stain, original magnification $\times 50$).

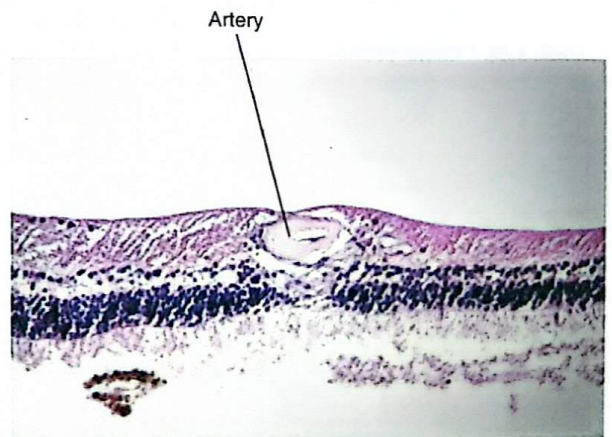


FIGURE 1.49 Cross section of the retina showing an infarction of a retinal artery. Again, the inner portion of the retina is thinner to the right compared with the left (H-E stain, original magnification $\times 50$).

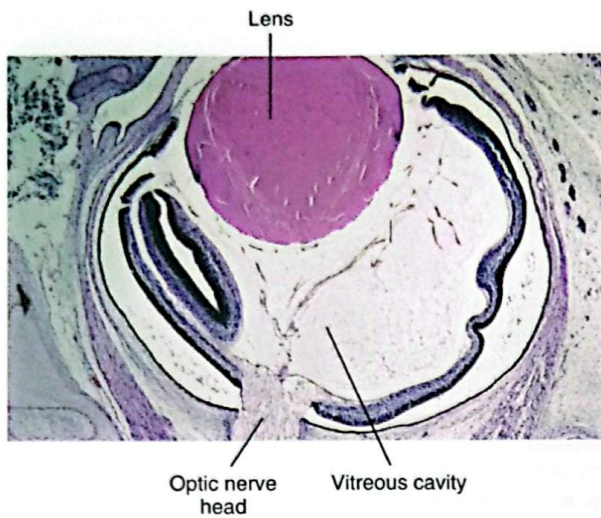


FIGURE 1.50 Eye of a fetus at the age of 10 weeks. Vascularization of the vitreous cavity arising from the optic nerve head is shown (H-E stain, original magnification $\times 10$).

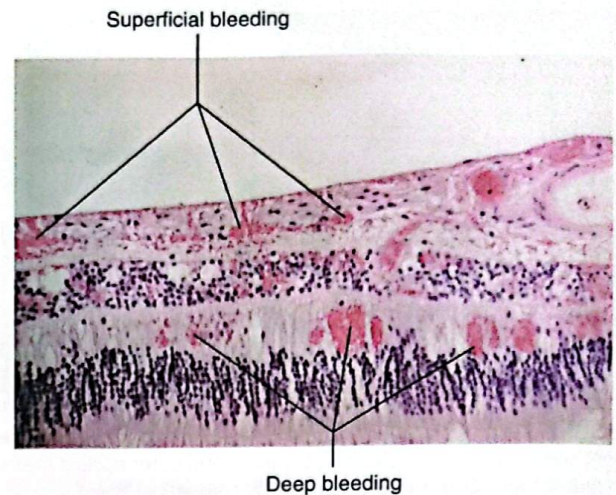


FIGURE 1.52 Hemorrhagic retinopathy after venous occlusion. Corresponding to the retinal architecture, deeper bleedings occur in the external plexiform layer of the retina in a locular manner (ophthalmoscopically spotlike). Bleedings in the superficial retinal layers line up with the nerve fiber layer (ophthalmoscopically flarelike appearance). In addition, a venous lumen is shown with a partially recanalized thrombus. (Courtesy B. Kirchhof, Cologne, Germany.)

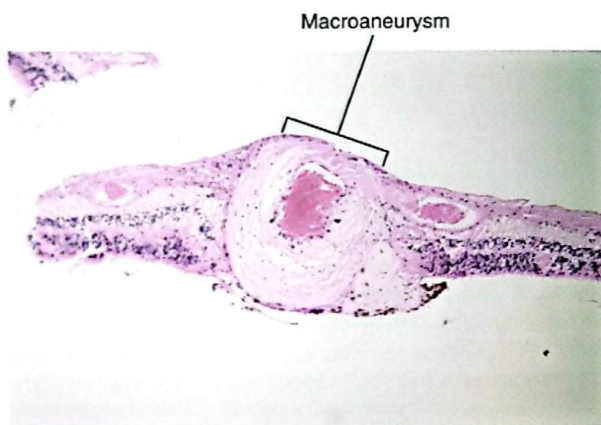


FIGURE 1.51 Cross section of the retina showing a macroaneurysm (H-E stain, original magnification $\times 25$).

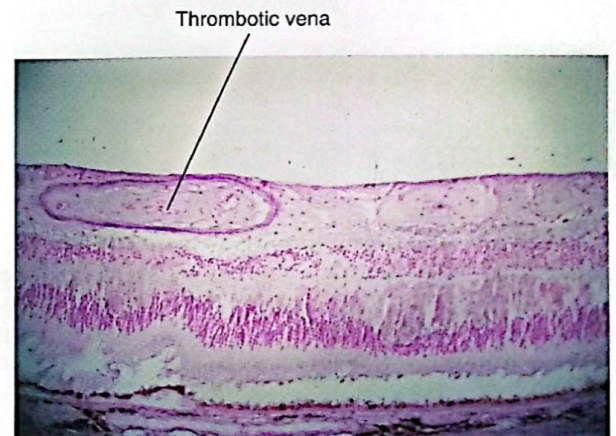


FIGURE 1.53 Thrombotic retinal parental vena barely recanalized (elastica stain). (Courtesy B. Kirchhof, Cologne, Germany.)



FIGURE 1.54 Same image as Figure 1.53 at higher magnification. Thrombotic retinal parental vena (elastica stain). (Courtesy B. Kirchhof, Cologne, Germany.)

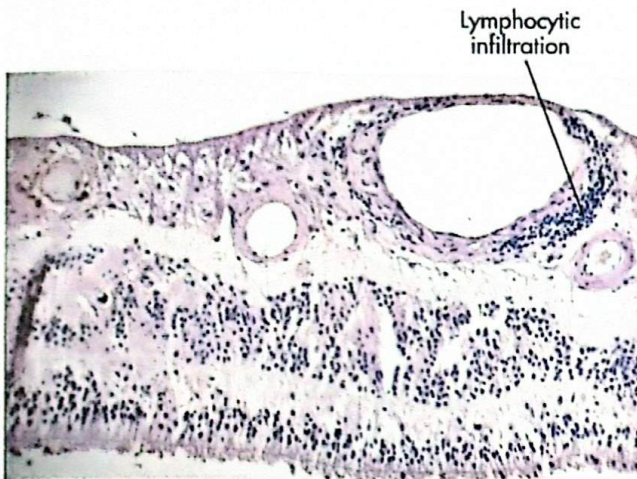


FIGURE 1.55 Periphlebitis: large lumen of a retinal parental vein with focal lymphocytic infiltration of the venous wall accentuated (H-E stain). (Courtesy B. Kirchhof, Cologne, Germany.)

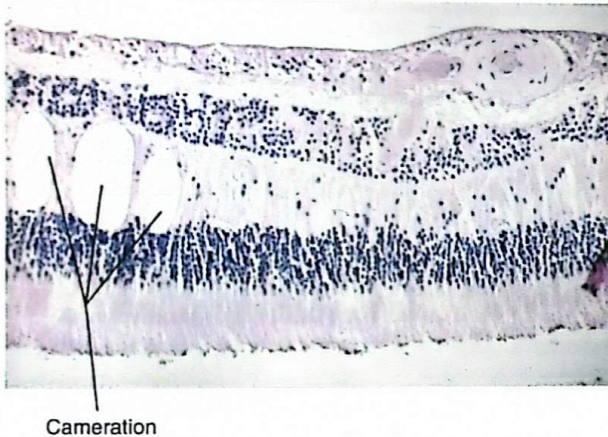


FIGURE 1.56 Completely thrombotic, smaller branch retinal vein in proximity of the macula with consecutive macular edema, identifiable by cameration of Henle's layer. (H-E) (Courtesy B. Kirchhof, Cologne, Germany.)

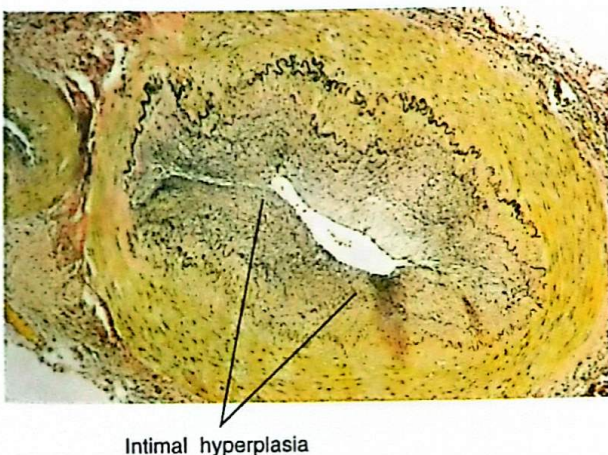


FIGURE 1.57 Cross section of a biopsy of a temporal artery with mild intimal hyperplasia and no signs of inflammation (Verhoeff–Van Gieson stain, original magnification $\times 25$).



FIGURE 1.58 Giant cell arteritis of the short posterior ciliary arteries: localized pattern dispersal of the muscular layer caused by chronic inflammatory lymphocytic and foreign body giant cell infiltration (H-E stain). (Courtesy B. Kirchhof, Cologne, Germany.)

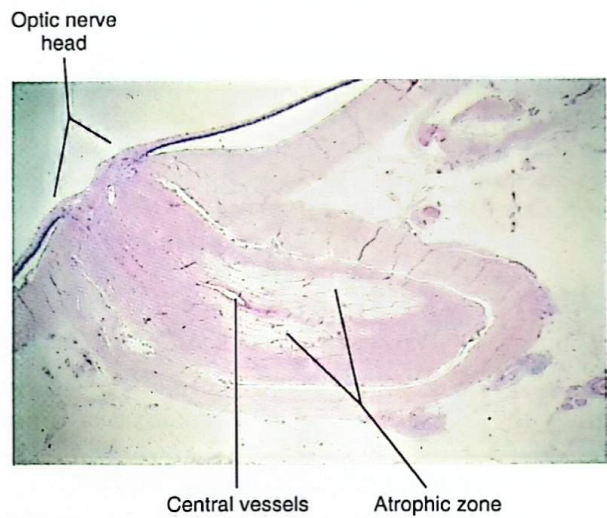


FIGURE 1.59 Partial optic nerve head atrophy in giant cell arteritis: longitudinal section of the optic nerve and papilla. Lightened zone surrounding the central vessels caused by nerve fiber atrophy (H-E stain). (Courtesy B. Kirchhof, Cologne, Germany.)

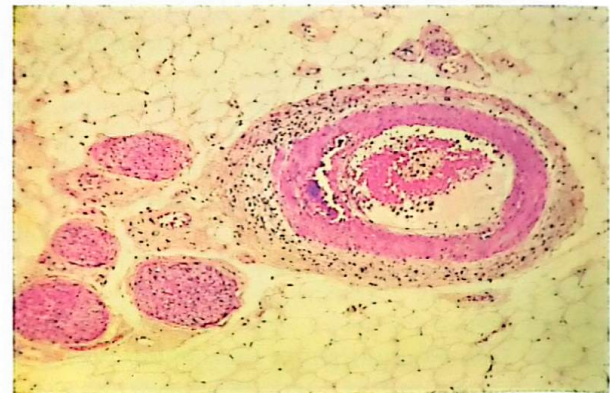


FIGURE 1.60 Another example of giant cell arteritis of the short posterior ciliary arteries with localized lamina muscularis dispersal following chronic inflammatory lymphocytic and foreign body giant cell infiltration (H-E stain) (see also Figure 1.58). (Courtesy B. Kirchhof, Cologne, Germany.)

Measurement of Blood Flow

From the most basic standpoint, the eye offers a unique opportunity to study hemodynamics. It is the only location in the body where capillary blood flow may be observed noninvasively in humans. Various factors influence the control and regulation of ocular blood flow, such as metabolic demands, blood nutrients, metabolic by-products, perfusion pressure, and blood gasses. The numerous interactions among these influences are complex, yet they must be studied to understand potential hemodynamic alterations in disease.

As seen in the first section, the ocular vasculature is an intricate structure. The various layers of tissue in the retina receive nourishment from both the uveal and retinal vasculature. The uveal circulation surrounds the retinal circulation in the globe, making it difficult to isolate the individual vascular beds. However, the two vascular beds have profound anatomic and regulatory differences, for example, highly fenestrated versus tight endothelial cell junctions and innervation versus noninnervation. The behavior of one ocular vascular bed does not predict the behavior of the other. Consequently, to determine the status of ocular hemodynamics in a patient, a comprehensive examination of ocular perfusion is necessary, with the contribution of each vascular bed of the eye evaluated separately.

Classic physiology teaches that blood flow is measured in milliliters per minute per gram of tissue. Only one commercially available technique can provide volumetric blood flow measurements in absolute units, and it is limited to measurements of flow in large retinal vessels. At this time, volumetric flow measurements in absolute units from retinal tissue and in the choroid are unobtainable. However, a number of hemodynamic measurement techniques can assess various aspects of blood flow in the retina, in the choroid, and in the vessels that supply each. Each of these techniques are examined in detail in this section.

Pulsatility Measurement Devices

The first blood flow assessment technique discussed is, at best, an indirect hemodynamic indicator. Measurements obtained with a blood pressure cuff may point to a stroke risk without any direct cerebral measurements

being made. Similarly, measurement of intraocular pressure (IOP) may provide insight into the hemodynamic status of the fundus.

Picture air being pumped into a tire with a puncture. Air surges in, and air leaks out. With each surge into the tire, there is a transient increase in tire pressure as the volume of air in the tire increases. Over time, the average volume of air in the tire does not change but only pulses up and down. Of course, the entire pulse of air into the tire is not reflected in the surge in volume, because when the pressure in the tire increases, so does the rate of air leaking out of the puncture. If the leak is never stopped, then air pulsing out offsets some unknown percentage of the air flowing into the tire. Can airflow into the tire be calculated from an air pressure measurement?

PULSATILE OCULAR BLOOD FLOW

Blood surges into the blood vessels of the eye during systole and continues to flow in more slowly during diastole. Similarly, blood pulses out of the ocular veins throughout the cardiac cycle, though at some delay in time relative to the inward flow from the arteries. It has been proposed that real-time measurements of IOP can be used to calculate the pulsatile component of blood flow. The pulsatile ocular blood flow (POBF) device (Figure 2.1; Paradigm Inc, formerly OBF Labs) is a pneumotonometer that measures IOP in real time. It is based on the principle (Figure 2.2) that blood volume in the eye increases with the systolic pulse and decreases during diastole. When the volume increases, eye pressure increases as well. If the relationship between eye pressure and eye volume is identical for everyone (Figure 2.3), then transient changes in IOP can be used to calculate absolute transient changes in ocular volume. As with the leaking tire, however, the true volume of blood entering the eye is unknown because the rate of venous flow (the leak) is not measured, is unknown, and varies among individual eyes. The IOP pulse wave is transformed into an ocular volume wave using the presumed universal relationship (Figures 2.4 and 2.5). The change in volume over time is reported as the POBF.

The POBF instrument is like a Goldmann applanation tonometer but uses air instead of mechanical pressure to



FIGURE 2.1

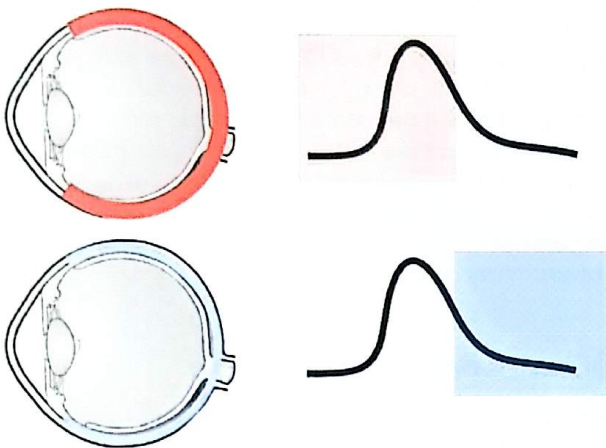


FIGURE 2.2

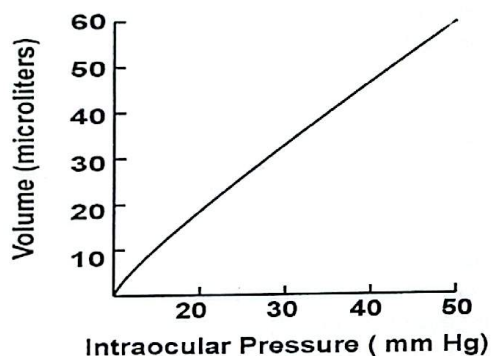


FIGURE 2.3

measure IOP. A pressurized tip is positioned in contact with the cornea, and air pressure within the tip is increased until the cornea is indented. By measuring the level of air pressure required to indent the cornea, IOP is measured (Figures 2.6 and 2.7). Individual pressure readings are taken at a rate of 200 per second. This rate is sufficiently rapid to allow real-time tracking of IOP

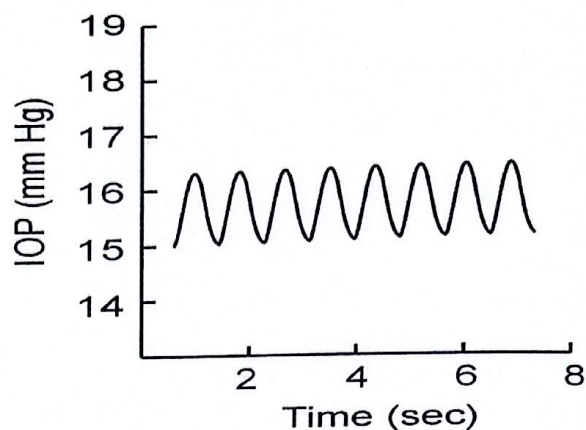


FIGURE 2.4

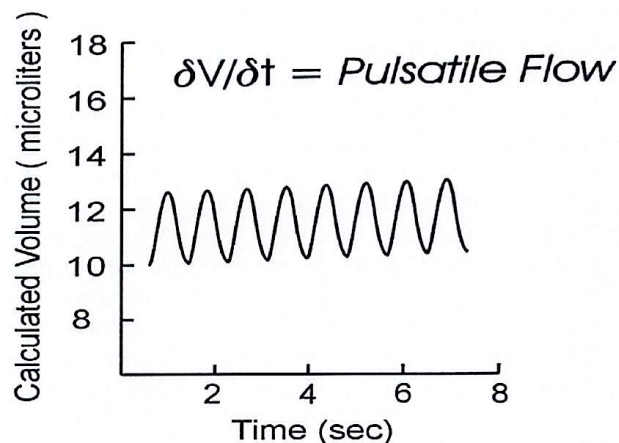


FIGURE 2.5

throughout the cardiac cycle (Figure 2.8). The patient is provided with a red fixation light within the center of the probe, delivered by a fiber-optic cable (Figure 2.9). As the measurement is acquired, the POBF device provides the user with an audio signal. If the probe is properly positioned, the pulsation in IOP can be heard, as well as observed on the POBF display (Figure 2.10). When the measurement is complete, the waveforms seen on the display can be printed, along with a detailed report containing the average IOP, IOP range, pulse amplitude, and calculated pulsatile component of ocular blood flow (Figures 2.11 and 2.12).

Several advantages and disadvantages are associated with the POBF technique. The greatest advantage is that the system is relatively inexpensive and affordable for the average small clinic. It also has been approved recently for Medicare reimbursement. The POBF device is simple to operate and requires no special training for anyone able to perform Goldmann tonometry (Figure 2.13). The greatest disadvantage of POBF is that it is not a direct measurement of blood flow (Figure 2.14). IOP is



FIGURE 2.6

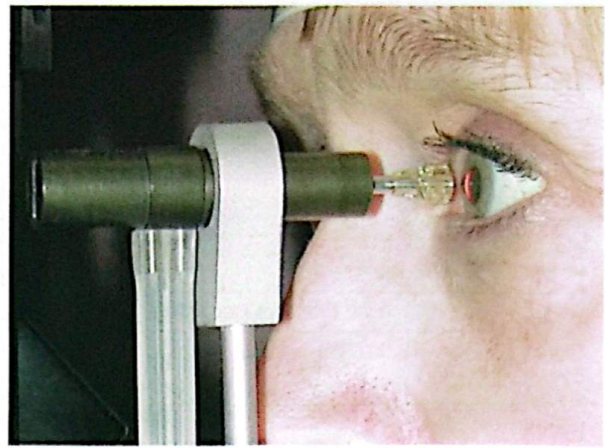


FIGURE 2.9

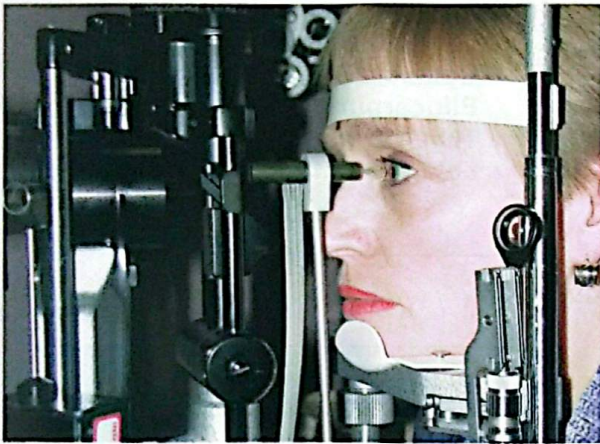


FIGURE 2.7

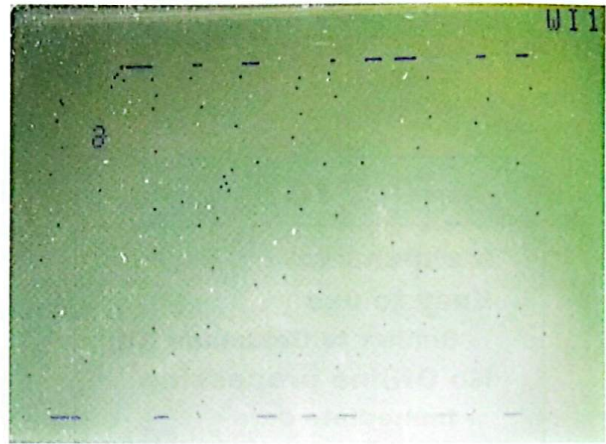


FIGURE 2.10

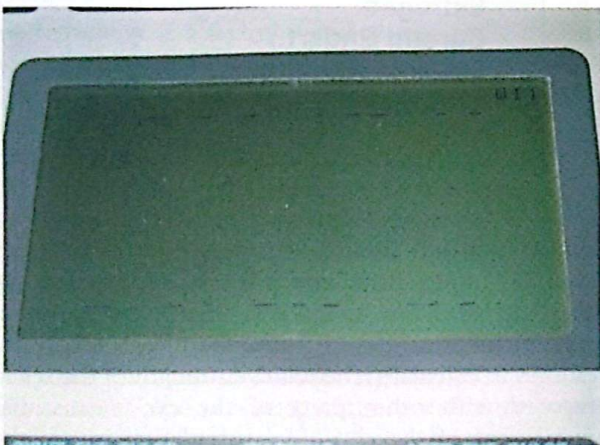


FIGURE 2.8

measured, and several assumptions about scleral rigidity and a universal IOP-eye volume relationship are made. Returning to the tire analogy, a large air pump and large leak could produce the same pulse in air pressure as a

Left Eye	Pulse:	1	2	3	4	5	Average
Minimum intraocular pressure	[mmHg]	15.5	15.4	15.7	15.2	14.5	15.3
Maximum intraocular pressure	[mmHg]	17.3	17.5	17.8	17.4	16.5	17.3
Average intraocular pressure	[mmHg]	16.4	16.4	16.7	16.3	15.5	16.3
Pulse amplitude	[mmHg]	1.9	2.1	2.1	2.1	1.9	2.0
Pulse volume	[μl]	3.8	4.2	4.2	4.4	4.1	4.1
Systolic time	[sec]	0.30	0.37	0.40	0.39	0.38	0.36
Diastolic time	[sec]	0.50	0.55	0.53	0.46	0.43	0.49
Pulse rate	[/min]	75	65	64	70	74	70
Pulsatile ocular blood flow	[μl/min]	601	608	640	681	749	656
POBF % Standard deviation							9

FIGURE 2.11

small air pump and a small leak. In the eye, large arteries and veins may provide large volumetric blood flow, which is indistinguishable from a lesser flow through smaller vessels.

POBF measurements have been performed in numerous studies of healthy subjects. Test-retest studies have found that the POBF produces highly reliable measurements, with men presenting with lower normal values than women (Figure 2.15). The 95% confidence

OBF Labs UK Ltd	
Crowsnest, Cleverton, Wilts. SN15 5BS. 0666 822269	
OBF Test recorded using OBF Labs (UK) Ltd Tonograph, Copyright 1992.	
The test was carried out with the patient at a slit lamp The right eye was recorded first.	
Name : EVANS, DAVE	Patient No.:
Date : 1.25.1995	D.o.B. : 07.17.56
Time : 17.18	Sex : M
Test No. : MC1007-102-4	

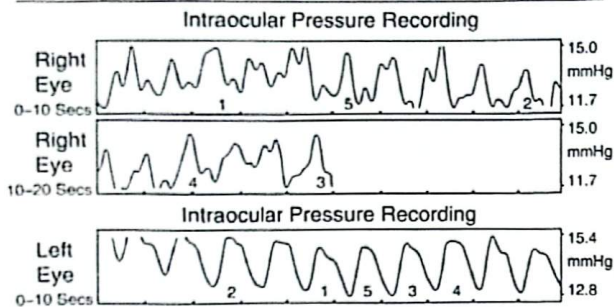


FIGURE 2.12

Pros
Inexpensive
Easy to use
- Similar to Goldmann IOP
No Offline processing
- Immediate data
Minimally invasive

FIGURE 2.13

Cons
Measures IOP
Is the pressure volume relationship universal?
Only measures pulsation
No diastolic measurement?
Coneal Contact

FIGURE 2.14

interval for normal data in men and women is shown in Figure 2.15. Many glaucoma medications have been studied using POBF (Figures 2.16 and 2.17). As with other methods, the POBF system has produced a wide range of results.

Reproducibility	
Reliability-	
Coefficient:	92%
Male mean:	669.9 ± 233.0
Female mean:	841.9 ± 254.6
Male 95% C.I.:	364 to 1266
Female 95% C.I.:	398 to 1346

FIGURE 2.15

Medications	
Levobunolol:	↑
Betaxolol:	↓
Pilocarpine:	No Effect
Timolol:	↓
Latanoprost:	↑

FIGURE 2.16

Health & Disease	
Age:	↓
Glaucoma NTG:	↓
Estrogen:	↑
Carotid Endart.:	↑
Diabetic Retinop:	↓
Choroidal Tumor:	↑

FIGURE 2.17

Systolic blood flow into the choroid causes the choroidal vasculature to increase slightly in volume. It is this fluctuation in eye volume that the POBF device presumes to calculate. The relative strength of the sclera compared with other parts of the eye means that engorgement of the choroidal vasculature causes the fundus to enlarge toward the center of the eye. One result of the fundus moving toward the center is a decrease in the distance between the fundus and cornea during systole. As the blood drains from the choroidal vasculature during diastole, the volume, as well as retina to cornea distance, is reduced to its original level (Figure 2.18). Therefore, as the fundus pulses throughout

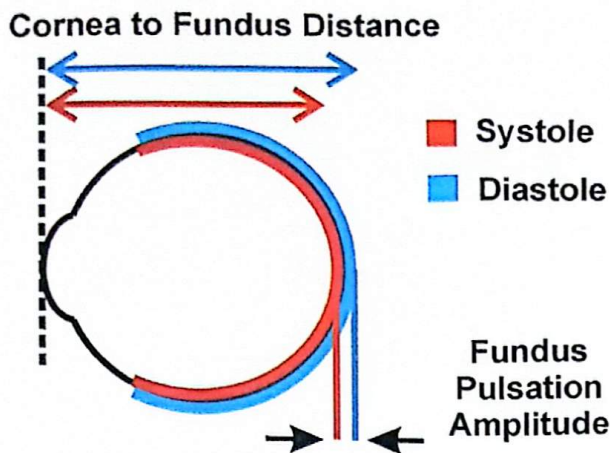


FIGURE 2.18

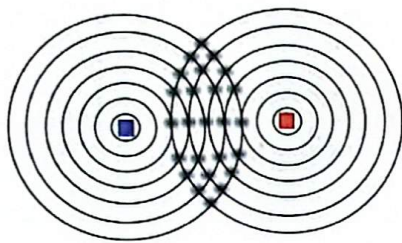


FIGURE 2.19

the cardiac cycle, the inner surface of the retina at the posterior pole moves toward and away from the cornea.

INTERFEROMETRY

Interferometry is a technique used to directly measure the pulsation of the fundus relative to the cornea. As implied by its name, interferometry is based on the interference pattern formed by two sources of light: one reflected from the fundus and one reflected from the cornea. The two beams are created from a single laser beam passing through the center of the eye. The beam is partially reflected by the cornea and also partially reflected by the retina (Figure 2.19).

Because the source of the two reflections is a single laser, the reflected light from each source has the same frequency. The result is a stationary interference pattern (Figure 2.20). The geometry of the interference pattern is a function of the distance between the two reflective sources. As the fundus pulses with the cardiac cycle, the location of the interference pattern moves. The magnitude of fundus pulsation can be calculated if the change in the interference pattern is known. This spacing is measured by the interferometer using a linear array detector (Figure 2.21). The detector quantifies the light level along its axis.

FIGURE 2.20

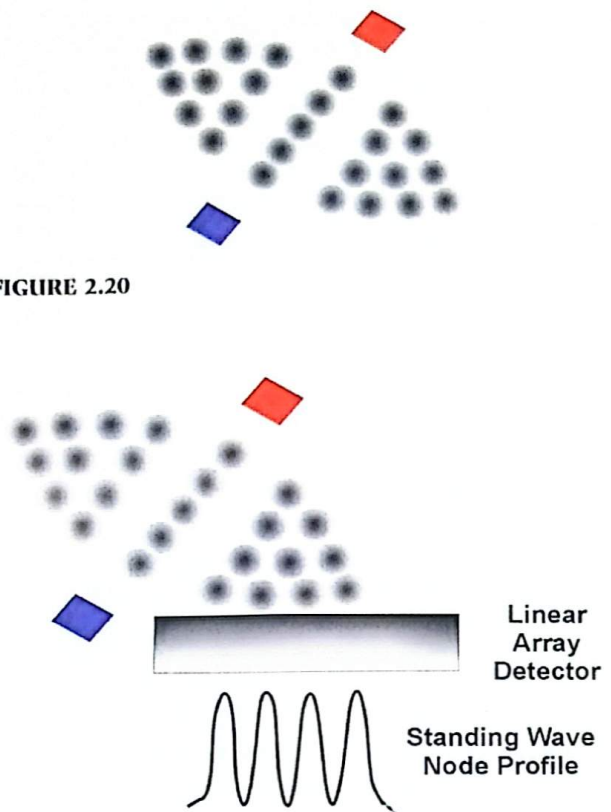


FIGURE 2.21

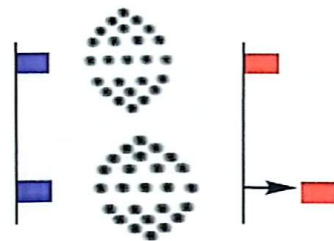


FIGURE 2.22

As the separation between two sources changes, position of the interference pattern also changes (Figure 2.22). If the interference pattern is measured in real time, changes in node spacing can be used to calculate the change in the relative position of the two wave sources (Figure 2.23). In the case of pulsations within the fundus, the pulsing fundus surface is displaced anteriorly as blood surges into the choroid. When this occurs, the relative distance between the surface of the fundus and the anterior surface of the cornea is decreased. If each surface acts as a reflector, the spacing within the resulting interference pattern will pulsate with the cardiac cycle.

The greatest advantage of the interferometry technique is that it measures fundus movement in micrometers and

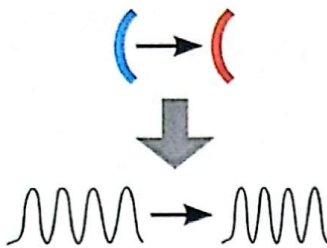


FIGURE 2.23

Pros
Direct measurement of fundus displacement Directly related to changes in choroidal blood volume Absolute measurement in micrometers

FIGURE 2.24

Reproducibility
Intraclass correlation coefficients: 0.95 to 0.98 Normal fundus pulsation amplitude: $3.9 \pm 0.3 \mu\text{m}$

FIGURE 2.25

is not a relative or unitless measurement. Very few of the technologies discussed in this section can quantify hemodynamic parameters in absolute terms (Figure 2.24). The other major advantage of this technique is that it has excellent reproducibility (Figure 2.25). The main disadvantage is that it is not commercially available. Currently, this device is only used by one laboratory (Figure 2.26). Another disadvantage is that the technique uses fundus pulsation as a surrogate for choroidal blood flow. The relationship between pulsation of the posterior pole relative to the corneal surface and volumetric choroidal blood flow is unknown.

The effects of various glaucoma medications on fundus pulsation have been tested by interferometry (Figures 2.27 and 2.28). Although several medications

Cons
Not commercially available yet... Not a direct blood flow measurement, but a "blood flow effect"

FIGURE 2.26

Medications
Acetazolamide: Nifedipine: Losartan: Isoprenaline: Betaxolol: Levobunolol:
↑ No effect ↑ ↑ No effect No effect

FIGURE 2.27

Medications II
Befunolol Metipranolol: Timolol: Clonidine: Dipivefrin: Pilocarpine:
↓ ↓ ↓ ↓ ↓ No effect

FIGURE 2.28

have been found to reduce fundus pulsation, the meaning of these results with respect to blood flow or, more importantly, retinal metabolism is unclear.

Pulsation has also been studied in relation to a number of diseases and in relation to age (Figure 2.29). Interestingly, pulsation increases in patients with diabetic retinopathy. Alterations that occur in retinal vasculature early in diabetic retinopathy include thickening of the basement membrane, alterations in elastin, and reduced collagen solubility. Each of these would tend toward less pliable ocular vasculature, confounding the clinical interpretation of altered fundus pulsation with regard to altered blood flow.

Health and Disease	
Age:	↓
Diabetic Retinopathy:	↑
Hyperinsulinemia:	↑
Peribulbar anesthesia:	↓
Elevated IOP	↓
Angiotensin II	no effect

FIGURE 2.29

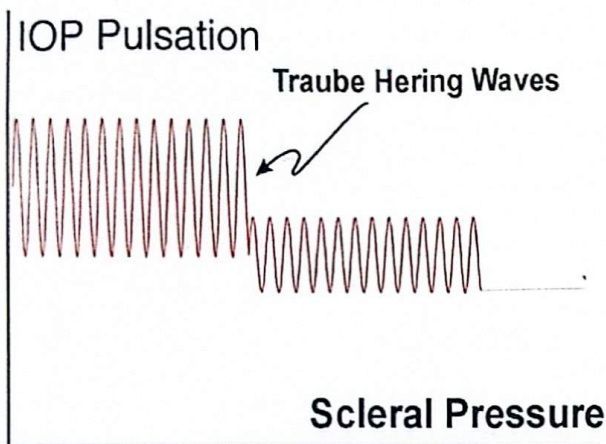


FIGURE 2.30

The oculo-oscillodynamography (OODG) device is a pneumotonometer that measures IOP in real time, similar to the POBF device (Figure 2.30). The OODG differs from the POBF in that it is used in combination with a scleral suction cup. During the measurement, IOP is increased. With sufficient IOP increases, flow ceases within each of the vascular beds within the globe (Figure 2.31). When blood flow ceases within a vascular bed, its contribution to the IOP waveform measured by the pneumotonometer disappears. The OODG uses this phenomenon to directly quantify the perfusion pressure within the uveal and retinal beds.

Several of the glaucoma medications studied using interferometry have also been studied with the OODG (Figure 2.32). In several cases, the interferometer identified reduced pulsation, but the OODG found no change. This may suggest that interferometry is more sensitive to small changes in ocular pulsation or that the local ocular mechanisms controlling fundus pulsation may differ from the systemic parameters that drive blood into the eye in the face of increasing IOP. The effect of internal carotid stenosis has also been studied with OODG (Figure 2.33).



FIGURE 2.31

Medications	
Timolol:	No effect
Betaxolol:	No effect
Carteolol:	Decrease
Pilocarpine:	No effect
Acetazolamide:	No effect

FIGURE 2.32

Health and Disease
Therapy normalizes reduced OODG in carotid stenosis
OAG subjects have normal ciliary perfusion pressure

FIGURE 2.33

Laser Devices

THE CANON LASER BLOOD FLOWMETER

The Canon Laser Blood Flowmeter (CLBF) (Canon U.S.A., Inc. One Canon Plaza, Lake Success, NY. 11042) is the only hemodynamic assessment device that can measure volumetric blood flow in absolute units. The CLBF is a Microsoft Windows®-based flowmeter that

uses two lasers to simultaneously measure blood velocity and vessel diameter. Blood flow is calculated from these two measurements (Figures 2.34 and 2.35). Used in a manner similar to a fundus camera, the CLBF provides an image of the fundus, from which the technician can target a large retinal artery or vein. The unit then performs measurements at the specified site.

The velocity measurement is based on the Doppler principle. When a light wave of frequency f_1 is scattered by a moving reflective source, the scattered wave has a different frequency, f_2 (Figure 2.36). In the case of the eye, moving blood cells are surrounded by stationary tissue. Light scattered by the tissue is not Doppler shifted and returns with the same frequency. Light reflected by moving blood cells is Doppler shifted and



FIGURE 2.34

returns with a slightly altered frequency. Light from these two reflective sources creates an interference pattern (Figure 2.37). Unlike the stationary pattern produced by two identical frequencies, the pattern produced by Doppler-shifted and non-Doppler-shifted light moves. The rate at which the interference pattern moves through space is determined by the difference in frequency of the two sources; a large difference in f_1 and f_2 produces a fast moving pattern, and a small difference in frequencies f_1 and f_2 produces a slow moving pattern. If the moving nodes are observed by a stationary detector, the resulting detector signal fluctuates, forming a time-based sinusoidal signal (Figure 2.38). In this simple example of two distinct frequencies forming an interference pattern, the rate at which the pattern passes the detector (the "beat" frequency)—and therefore the frequency of the resulting signal produced by the detector—is equal to the frequency difference of shifted and nonshifted frequencies ($f_1 - f_2$) (Figure 2.39). This fact is used to determine the various Doppler-shifted frequencies contained in the interference pattern.

When the frequency of the Doppler shift is known, the velocity of the moving reflective particle can be calculated. The Doppler shift equation is presented in Figure 2.40. The Doppler shift is equal to 2 times the velocity of the reflective source (erythrocytes in the case of blood flow) multiplied by the cosine of the angle between the velocity and light vectors, all divided by the wavelength of nonshifted light. With laser Doppler, the wavelength of the incident beam is known, and the Doppler shift is calculated by analyzing the beat



FIGURE 2.35

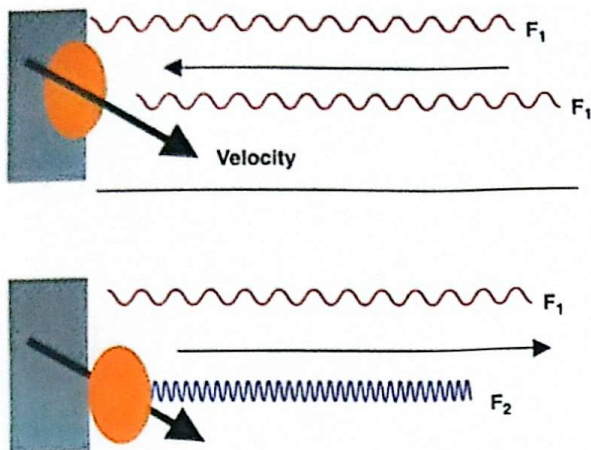


FIGURE 2.36

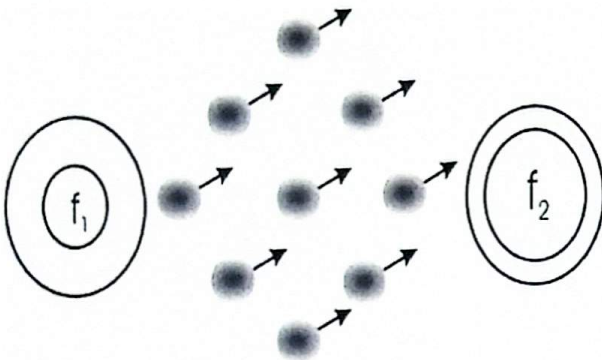


FIGURE 2.37

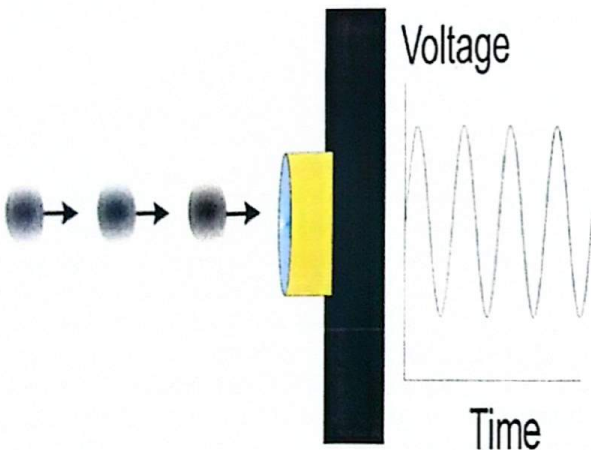


FIGURE 2.38

frequency from the resulting interference pattern. The missing piece of information is the angle between the incident beam and the velocity vector of the moving blood.

The CLBF uses an innovative solution that allows the unit to deduce the orientation of the blood vessel under

**Interference frequency
Voltage equals Doppler
frequency**

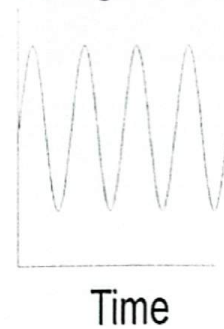


FIGURE 2.39

Doppler and Angle

$$\text{Shift} = \frac{2V_{\text{Blood}} \cos \theta}{\text{Wavelength}}$$

FIGURE 2.40

investigation. Two parallel photomultiplier tubes are used to sample Doppler-shifted light (Figure 2.41). Because the magnitude of Doppler shift is a function of the angle between the motion and observer (see Figure 2.40) and the additional angle (alpha) between the reflective source and two detectors is known (Figure 2.41), the detectors observe two different levels of Doppler shifts. The ratio of Doppler shifts observed is proportional to a combination of the known and unknown angle (Figure 2.42). The equation in Figure 2.42 can be solved for the angle, theta, which is required for a calculation of absolute blood velocity. In a complicated system (i.e., the real world), the signal contains a large number of velocities. The CLBF uses Doppler shifts to identify the fastest moving blood particles and uses the fastest velocity to calculate the average velocity.

Similar to a fundus camera, the CLBF has a chin rest and forehead bar for the patient (Figure 2.43). The height is adjusted so that the lateral canthus is approximately level with an indicator line of the frame of the headrest (Figure 2.44). Eye position is controlled by manipulating a fixation target (Figure 2.45, the black cross) within the unit. While the technician is preparing

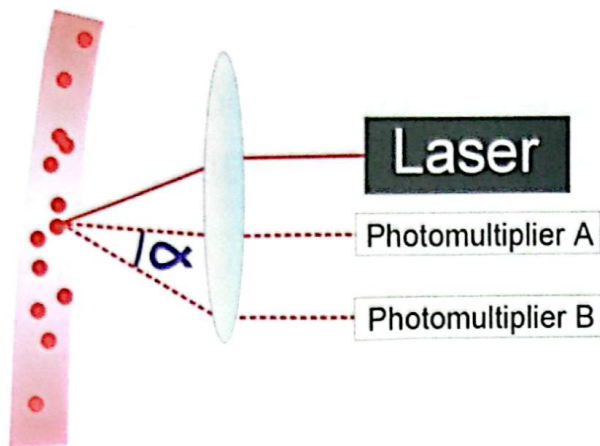


FIGURE 2.41

CLBF Bi-Directional Optics	
$\frac{\text{Shift A}}{\text{Shift B}}$	$= \frac{\cos\theta + \alpha}{\cos\theta}$

FIGURE 2.42

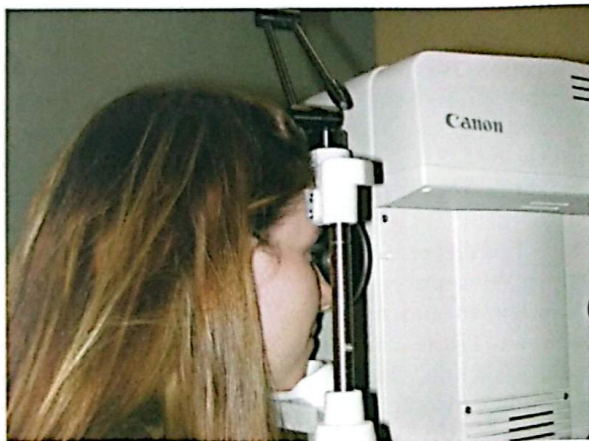


FIGURE 2.43

to acquire an image, the patient sees a fixation target and a green laser line (used to measure vessel diameter) on a yellow field.

The technician has an option of viewing the fundus image on the computer monitor or through the camera's viewfinder (Figure 2.46). Patient compliance is easily monitored, as the fixation target should be

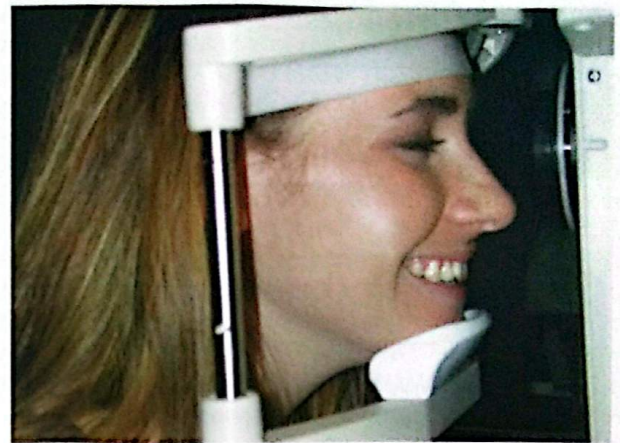


FIGURE 2.44

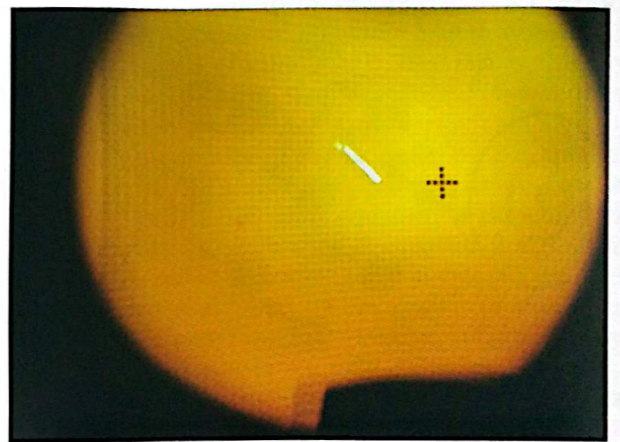


FIGURE 2.45

centered on the macula if the patient is focusing on the target. The CLBF software requires the user to enter the correct eye for examination (Figure 2.47). By sensing the camera position relative to the headrest, the CLBF will not take an image in the wrong eye. The software also requires the user to enter the position of the area to be analyzed (superior, inferior, temporal, etc.) and displays the location and orientation of the measurement bar (green laser line) relative to the macula. By moving the fixation target, the vessel of interest is positioned in the center of the image (Figure 2.48).

Camera alignment and distance to the eye are critical for an accurate measurement. To ensure proper positioning, the CLBF displays two yellow flashing triangles (Figure 2.49) on the image. The camera position is gently adjusted on each axis (laterally, superior/inferior, anterior/posterior) until the flashing yellow triangles are in sharp focus and positioned at each edge of the image. If there is difficulty in obtaining a clear, sharp image, the Doppler data may



FIGURE 2.46

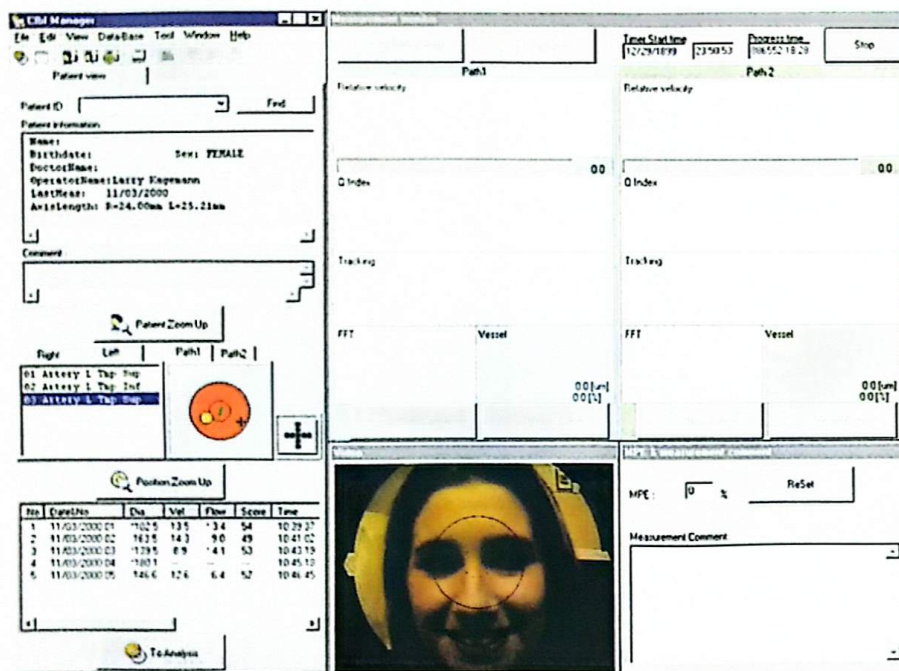


FIGURE 2.47

exhibit noise and be of poor quality. The CLBF allows the user to select a "high-intensity" laser setting for patients with poor optics, such as would result from cataract formation (Figure 2.50). After data has been acquired, the Doppler waveforms appear in the top right quadrant of the computer display (Figure 2.51). If the quality of the data is acceptable, the waveforms should resemble the cardiac cycle, and the quality control indicator bar (seen between the Doppler

waveform and diameter display) should be in the green area.

Each blood flow measurement requires two sets of data. Once the data is acquired, blood flow and velocity figures are calculated. These figures can be displayed in tabular form along with vessel diameter measurements and data quality scores (Figure 2.52). From the table, both the waveform of any individual measurement as well as the measured velocity at any



FIGURE 2.48

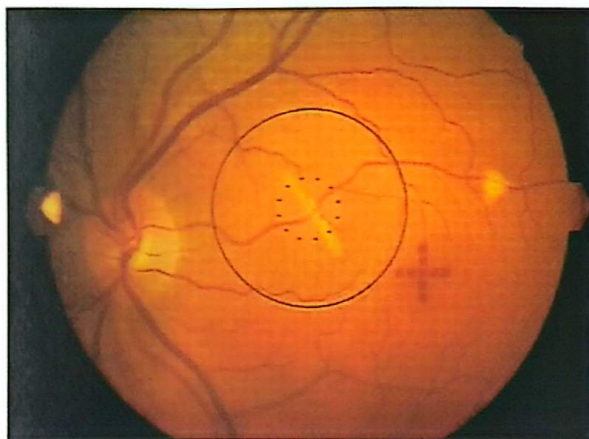


FIGURE 2.49



FIGURE 2.50

selected point along that waveform, can be displayed (Figure 2.53).

The CLBF is the only blood flow device currently available that can calculate volumetric blood flow to the retina. The system is an improvement over older laser technologies that could not track vessels or maintain the Doppler sampling laser position automatically on the center of the vessel. Furthermore, older versions of this velocity and diameter measurement combination did not allow simultaneous measurements; instead, they required Doppler sampling with one device and diameter imaging with another (Figure 2.54).

The CLBF has several weaknesses (Figure 2.55). The biggest is an assumed relationship between the

maximum Doppler shift and the true average blood velocity. In a turbulent flow system, the average velocity is equal to the maximum velocity. In a laminar flow system, the average velocity is half of the maximum. The CLBF uses something in between these two values. Although it may be a good assumption, it is still an assumption and depends heavily on the measurement location used. Areas with a high degree of tortuosity or near branch points will tend to be more turbulent, whereas vascular areas that are relatively linear and free of branches will tend to be closer to laminar flow. No single relationship exists between the maximum velocity (measured by CLBF) and the average velocity (used to calculate flow).



FIGURE 2.51

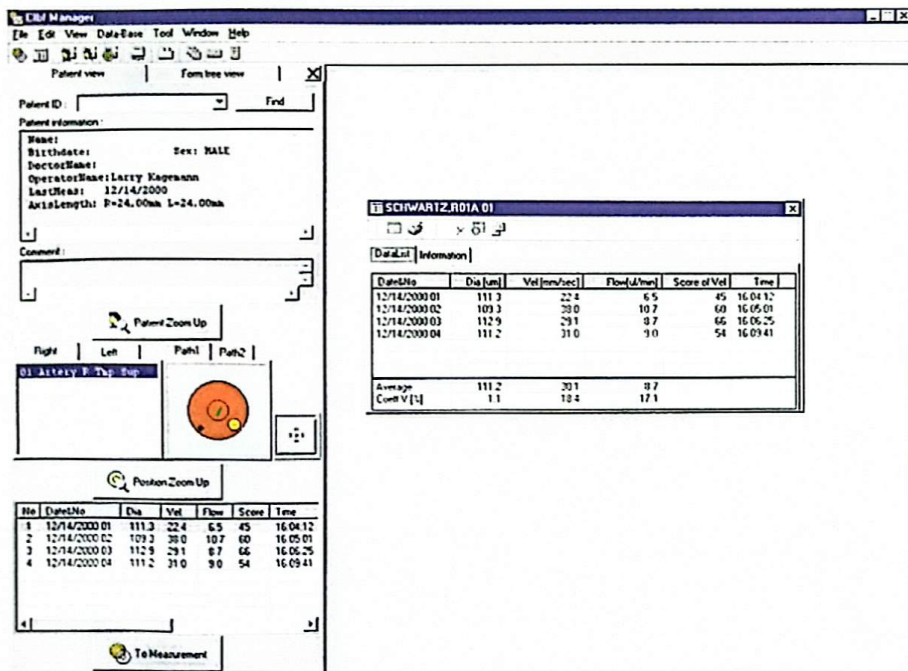


FIGURE 2.52

Several validation studies have been performed on the CLBF (Figures 2.56 and 2.57). When using a device in clinical research, it is vital to first document the reproducibility of the new measurement technique. Coefficients of variation for CLBF data differed between users, ranging between 16% and 22%—levels that are high but acceptable for research when taken into account during the design of a study. A second study compared CLBF flow measurements in retinal arteries with the average flow

velocity measured in the central retinal artery by color Doppler imaging (CDI). A significant correlation was observed; low flow values measured in the retina by CLBF corresponded with low velocities measured in the central retinal artery by CDI. Even though the CLBF measurements had both diameter and velocity components, the agreement between the two devices tends to suggest that the CLBF is sensitive to different levels of blood velocity as measured by Doppler shifts in laser light.

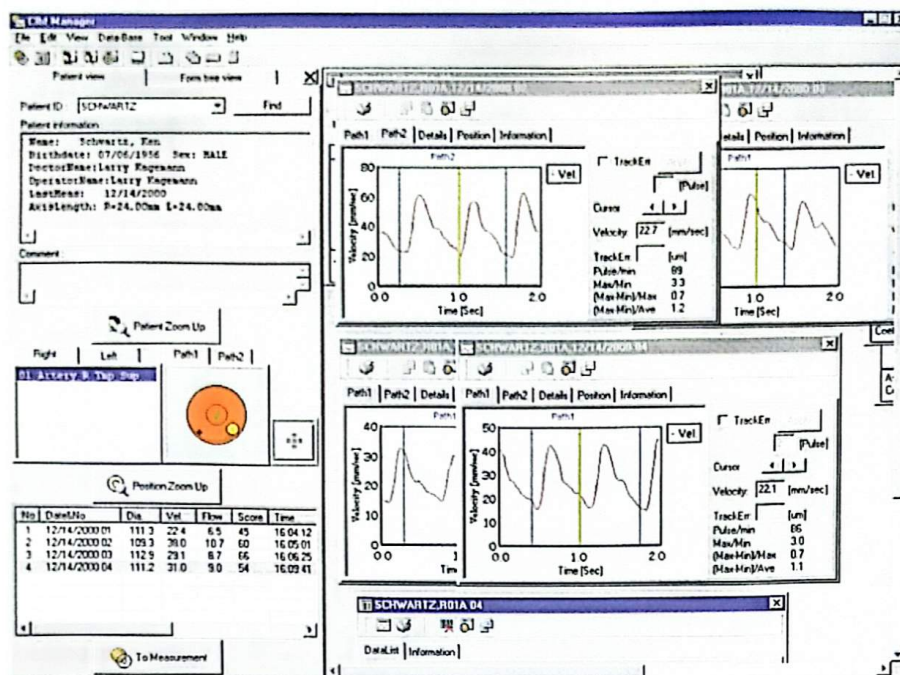


FIGURE 2.53

Pros

Measures volumetric bloodflow
Vessel tracking
Simultaneous vessel diameter
and velocity measurements

FIGURE 2.54

Cons

Mean velocity is assumed to
be 1.6 times the maximum
Flow is calculated,
not measured

FIGURE 2.55

Validation 1

	Observer 1			Observer 2		
	CoV	SD	RG	CoV	SD	RG
Diameter	5.33	2.75	1.18 - 10.01	7.71	8.89	1.01 - 27.30
Velocity	17.23	11.01	10.53 - 39.81	15.88	14.36	1.57 - 45.04
Flow	21.41	10.73	8.0 - 39.36	15.97	18.17	0.01 - 66.41

CoV = mean coefficient of variation (%),
SD = standard deviation (%), RG = range (%)

FIGURE 2.56

Validation 2

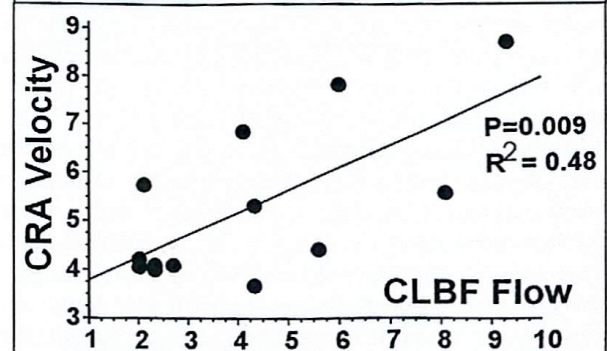


FIGURE 2.57

Angiography

FLUORESCEIN ANGIOGRAPHY

Scanning laser ophthalmoscopes are capable of a wide range of imaging applications in ophthalmology (Figure 2.58 to 2.60). The Heidelberg retina angiography (HRA) system is a digital imaging platform equipped with argon and near infrared lasers (Figure 2.58). The Rodenstock scanning laser ophthalmoscope (SLO) is another imaging device that produces images of the fundus (Figure 2.59). Equipped with argon, infrared, and helium-neon lasers and many apertures and filters, the SLO has a large number of imaging modes.

Both the HRA and SLO use a confocal optical system (Figure 2.61). For each point of the image, light is focused to a point on the fundus. Light reflected from this point is quantified by a photodetector. Confocal systems create sharp images by blocking scattered light from the image (Figure 2.61). Only light from the point of interest is focused to a point at the hole in the confocal

aperture. After passing through the optics, scattered light from adjacent reflective sources is blocked by the confocal filter (Figure 2.62). Combined with excellent optics, the SLO produces incredibly clear images of the fundus. In the 20° red-free image in Figure 2.63, the texture of the nerve fiber layer is clearly visible. Figure 2.64 is an example of a 40° red-free fundus image from a healthy volunteer.

The HRA and SLO are also used to quantify retinal hemodynamics. By recording fluorescein and indocyanine green angiograms, both the SLO and HRA systems provide valuable data on the movement of blood through the retinal and choroidal vasculature; however, measurement of volumetric blood flow by angiography is currently impossible.

To perform SLO angiography, the patient is first seated comfortably with the chin in the chin rest and forehead against the bar (Figure 2.65). No fixation target is provided during SLO angiography. The fellow eye gazes into the frame of the SLO (Figure 2.66) while the eye being examined looks into a field of light (Figure 2.67).



FIGURE 2.58



FIGURE 2.60



FIGURE 2.59

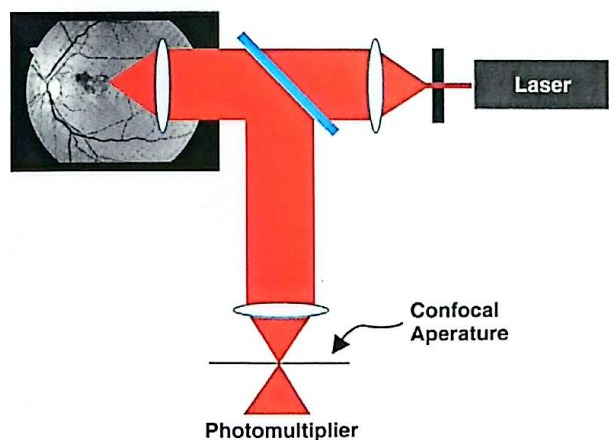


FIGURE 2.61

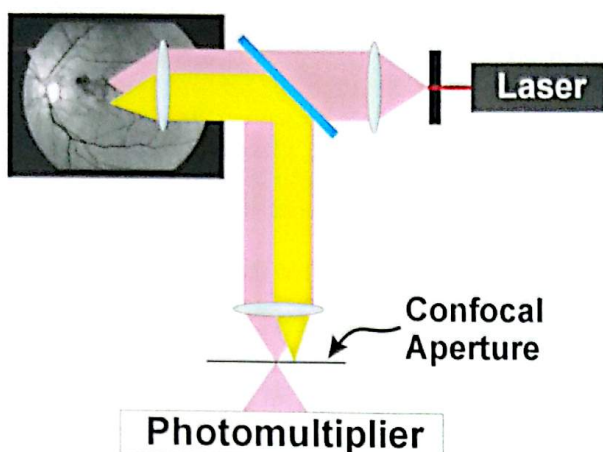


FIGURE 2.62



FIGURE 2.65

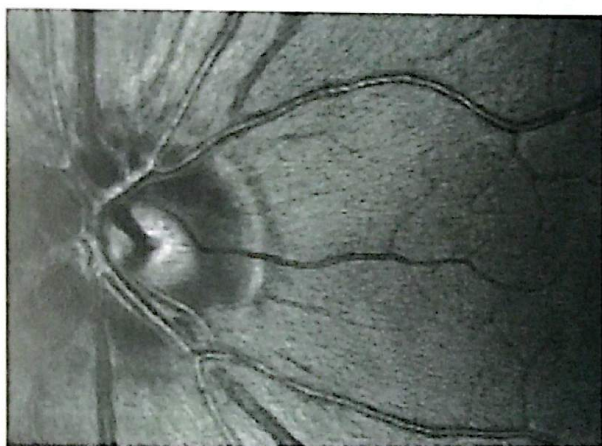


FIGURE 2.63



FIGURE 2.66

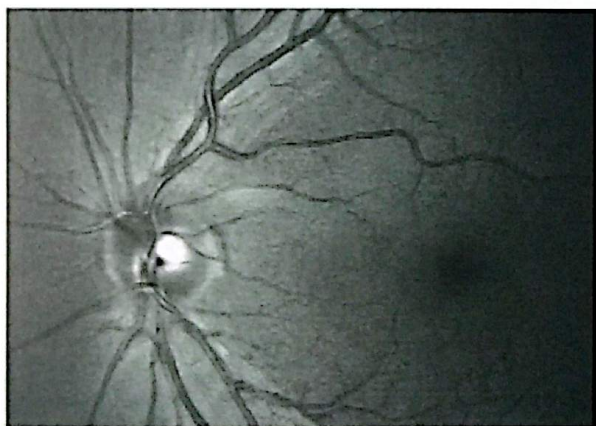


FIGURE 2.64

Because of the size of the instrument, alignment of the eye must be accomplished by verbal commands to the patient. The red-free image seen in Figure 2.63 was obtained by asking the patient to look slightly nasally and

downwards. With no fixation target or precise eye movements necessary for proper alignment, it is necessary for patients to concentrate while keeping their head motionless during the examination. In addition, patients must make small precise adjustments in gaze, while keeping their eyes wide open in the face of constant high illumination and receiving injection of dye through an antecubital vein. A cooperative patient is vital for the production of high-quality angiography sequences.

To operate the SLO, the technician works through a Microsoft Windows®-based interface (Figure 2.68) program. The SLO program consists of a laser control panel on the right of the screen (Figure 2.69) and an image recorder window displayed in most of the screen (Figure 2.70). If desired, the image quality can be observed through a higher quality auxiliary monitor, as seen in the center of the table in Figure 2.71. To the right of the second video monitor is a Super VHS video cassette recorder (VCR) and a time encoder with a 1/100 second resolution. In testament to its versatility, the SLO provides several more video-output channels

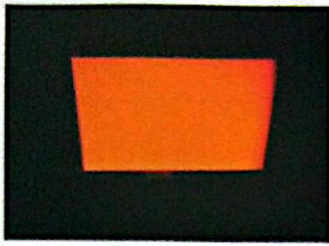


FIGURE 2.67

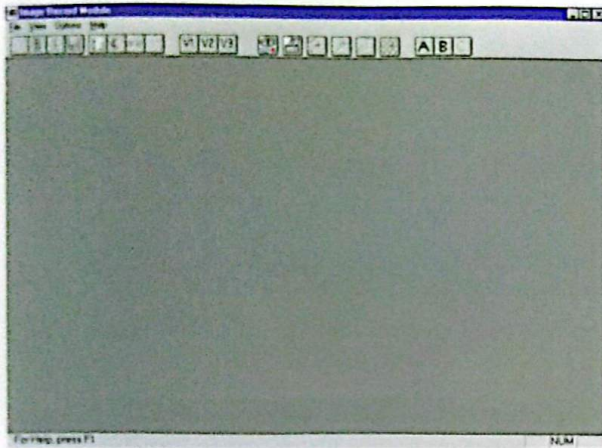


FIGURE 2.68

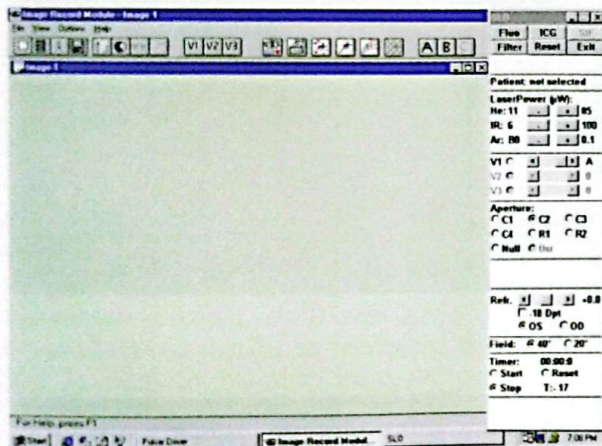


FIGURE 2.69

that are not used in the configuration in Figure 2.71, as well as video-input channels. The video inputs allow innovative experimentation, providing the user with the ability to project video images directly onto the retina while monitoring their position in the SLO image. Projection of an image directly onto the retina would allow the operator to visualize the area of the retina reacting to light.

To perform fluorescein angiography (FA), a butterfly needle is placed into an antecubital vein (Figure 2.72).

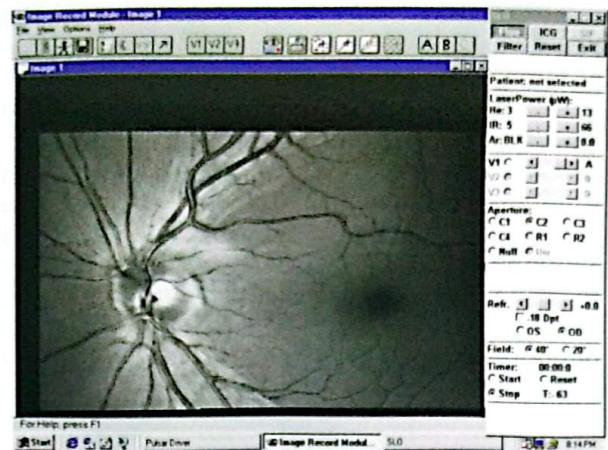


FIGURE 2.70



FIGURE 2.71

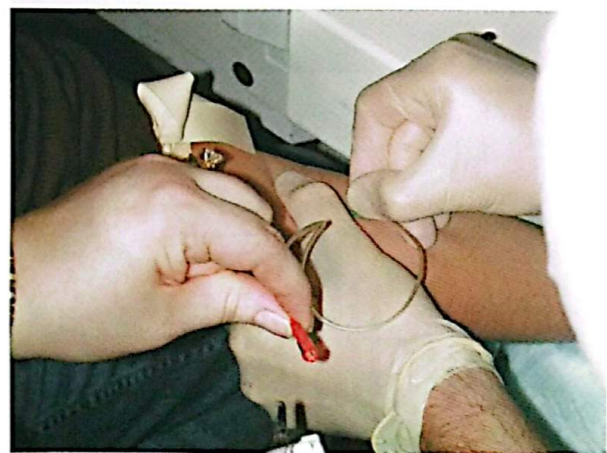


FIGURE 2.72

Fluorescein dye, 5 cc, and a 10-cc saline flush are connected to the needle through a stopcock (Figure 2.73). Before injection of the dye, an angiography filter is placed into position within the SLO. The filter blocks reflected

laser light while allowing light emitted by the stimulated dye to pass through to the SLO photodetector (Figure 2.74). A rapid injection of dye is immediately followed by a saline flush. The filling phase of a 40° angiogram is seen in Figures 2.75 through 2.80.

An optical version of dye dilution analysis is performed on the recorded angiogram. Dye dilution experiments are designed to calculate total blood volume. A known amount of a chemical marker is injected into a vein, and the concentration of the dye in an artery is monitored in real time. The first experiments were accomplished in 1929, by performing a series of blood draws, collecting one sample per second into vials on a rotating drum (Figure 2.81). Analysis was performed, and the concentrations of the marker were graphed (Figure 2.82). With ophthalmic angiography, the concentration of dye is represented by the fluorescence level, that is, the brightness of the image. Fluorescence is graphed against time to form a dye dilution curve. Figure 2.83 shows two curves, each



FIGURE 2.73

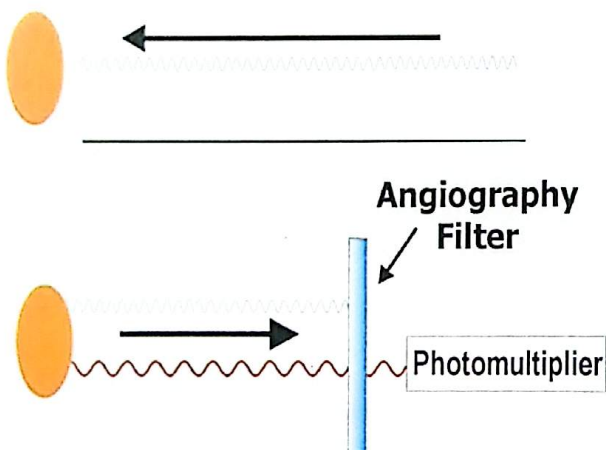


FIGURE 2.74

consisting of optical samples obtained at two positions on a retinal artery. The separation in time represents the amount of time required for dye to travel from the first to second position on the vessel. When this is

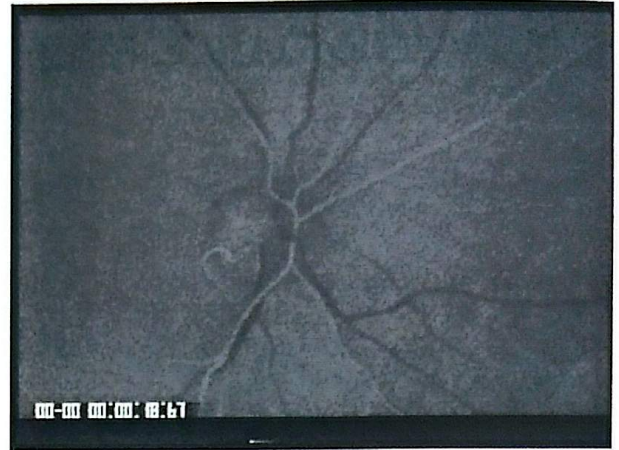


FIGURE 2.75

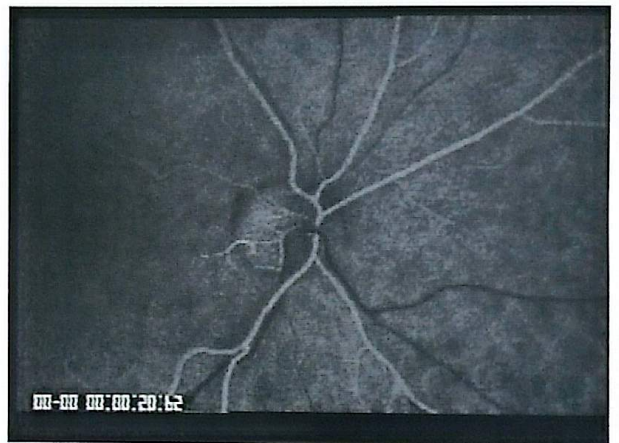


FIGURE 2.76

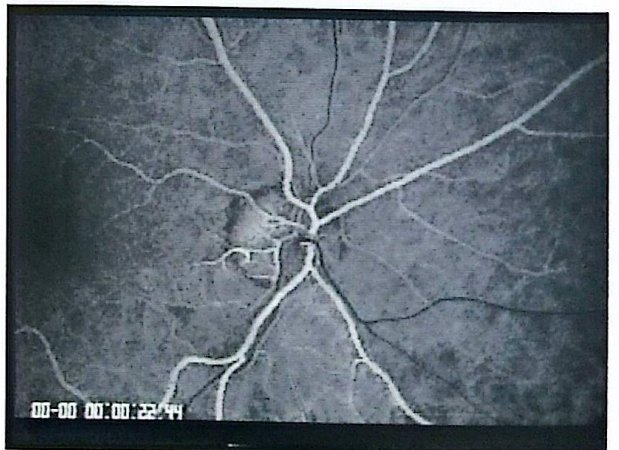


FIGURE 2.77

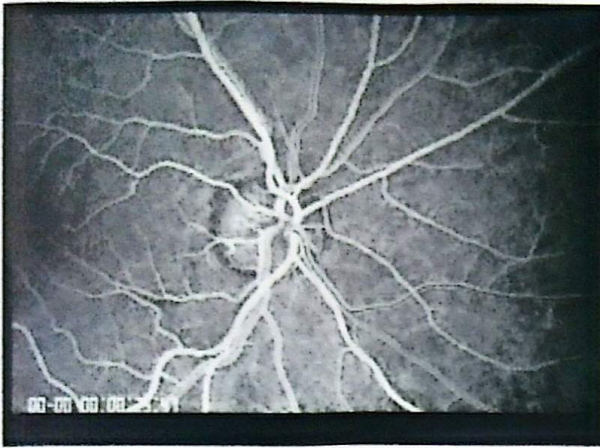


FIGURE 2.78

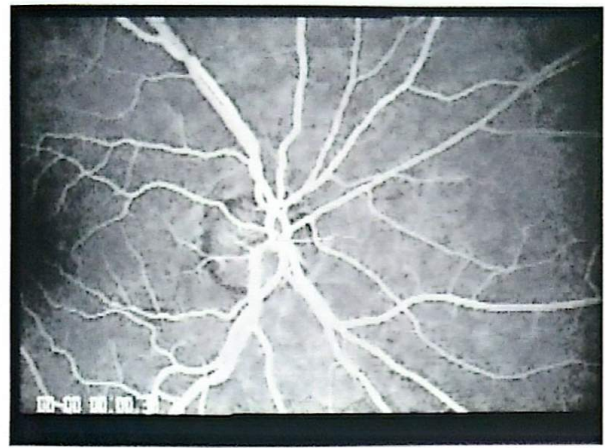


FIGURE 2.80

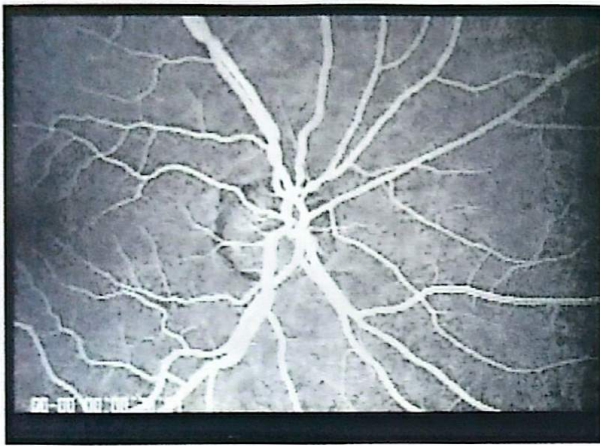


FIGURE 2.79

combined with a distance measurement (Figure 2.84), a mean dye velocity can be calculated. If two curves are obtained, one from an artery and the other from the corresponding retinal vein (Figure 2.85), the difference in time between the curves represents the amount of time necessary for blood to travel through the retinal vasculature in that quadrant. This is the arteriovenous passage (AVP) time.

To produce dye dilution curves, it is necessary to optically sample the brightness at the center of the vessels recorded on the video. Analysis is performed on a Mac G4 computer equipped with a scientific frame grabber and custom written software, and a Super VHS VCR (Figure 2.86). After the filling segment of the FA is digitized, the brightness of an artery and vein pair in each frame is sampled. This is done by manually placing a 5×5 pixel sample window on the center of the vessel in every frame of the dye arrival video and then calculating the average value of the pixels contained within (Figure 2.87). The image is magnified to ensure placement within the vessel boundaries and to avoid including the surrounding tissue (Figure 2.88). If a good deal of eye

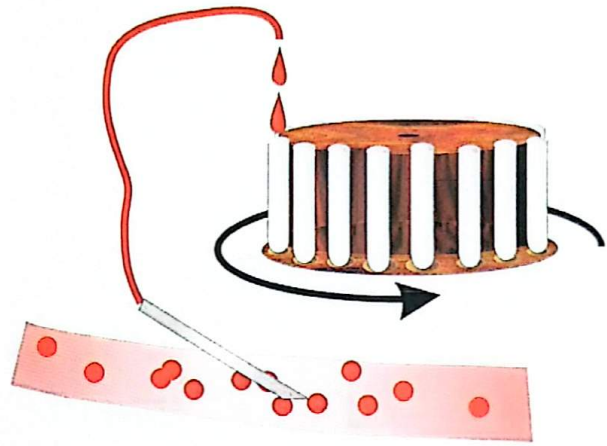


FIGURE 2.81

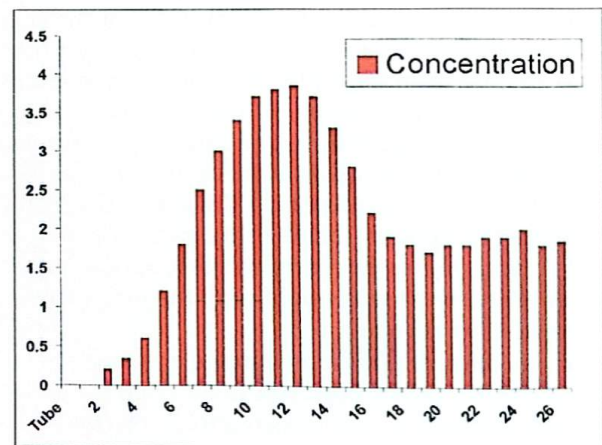


FIGURE 2.82

movement occurs during the filling phase, image magnification must be limited to ensure that the measurement area remains within the window after saccades. If the eye remains stationary during dye filling, a

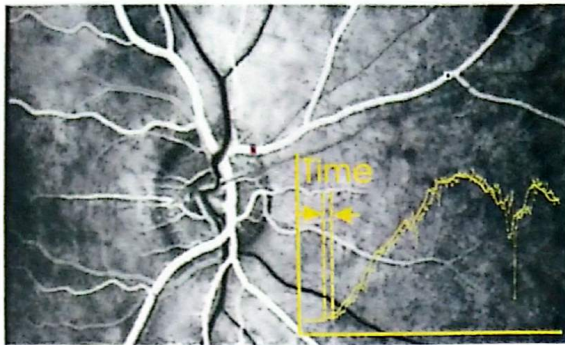


FIGURE 2.83

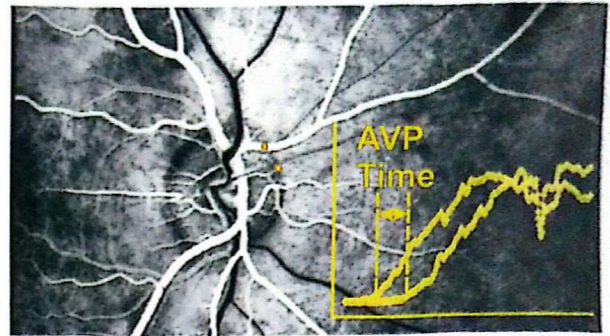


FIGURE 2.85

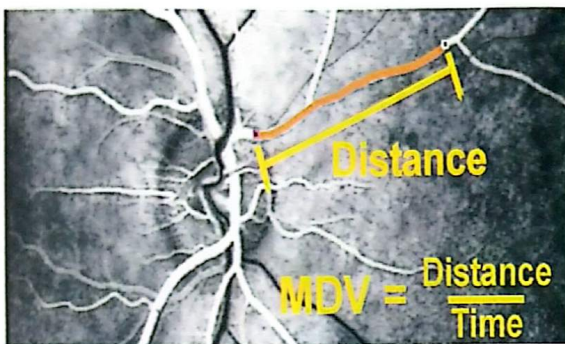


FIGURE 2.84

high magnification may be used (Figures 2.88, 2.89). Note that the 5×5 pixel sample area nearly fills the vessel (Figure 2.90). There is only a 1 or 2 pixel window of error for sample placement before the sample begins to include the surrounding tissue in the measurement (Figure 2.91). In the case of the vein, the box is placed near the edge of the vessel. This ensures that the sample contains both blood and dye from the center of the vein, representing dye returning from the peripheral retina, as well as blood near the edge of the vein, representing dye returning from capillaries near the disc. If the sample were limited to the 2 or 3 square pixels near the edge of the vein, where dye first appears, the AVP time would be close to zero. Further, measurement of the first appearance in the periphery of the vein would limit the measurement to peripapillary circulation.

The dye dilution plots represent the brightness in the vessel, as well as some degree of noise (Figure 2.92). A statistical method is used to determine objectively the precise frame of dye arrival. The yellow line in Figure 2.93 represents the upper limit of a 95% confidence interval calculated from the baseline artery brightness levels. When two of three frames contain fluorescence levels above the 95% confidence interval, the first of those frames is identified as the dye arrival frame. A similar limit is calculated for the vein. This analysis



FIGURE 2.86



FIGURE 2.87

procedure is performed for the temporal superior and inferior artery and vein pairs (Figure 2.94).

The greatest advantage of dye dilution analysis over other techniques is that it has proven to be sensitive to small changes in retinal hemodynamics. The average number of frames between arterial and venous dye



FIGURE 2.88

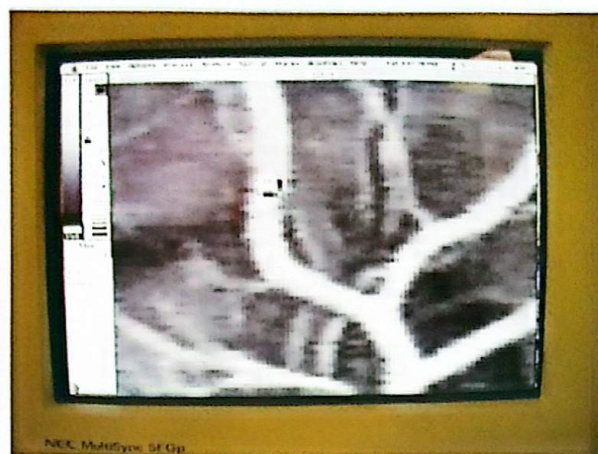


FIGURE 2.90

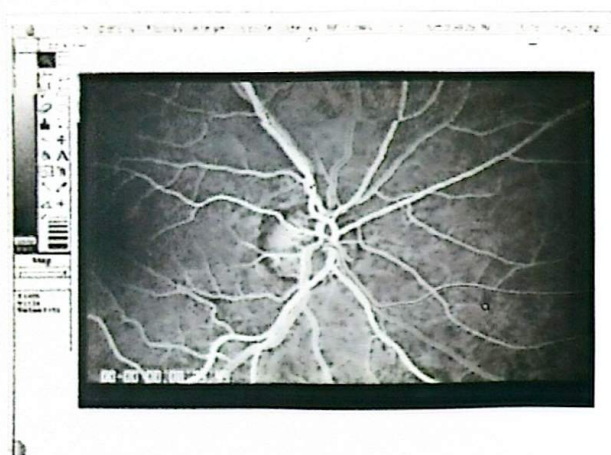


FIGURE 2.89

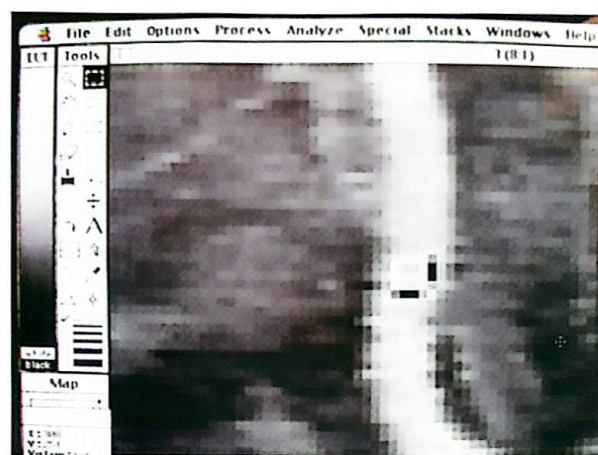


FIGURE 2.91

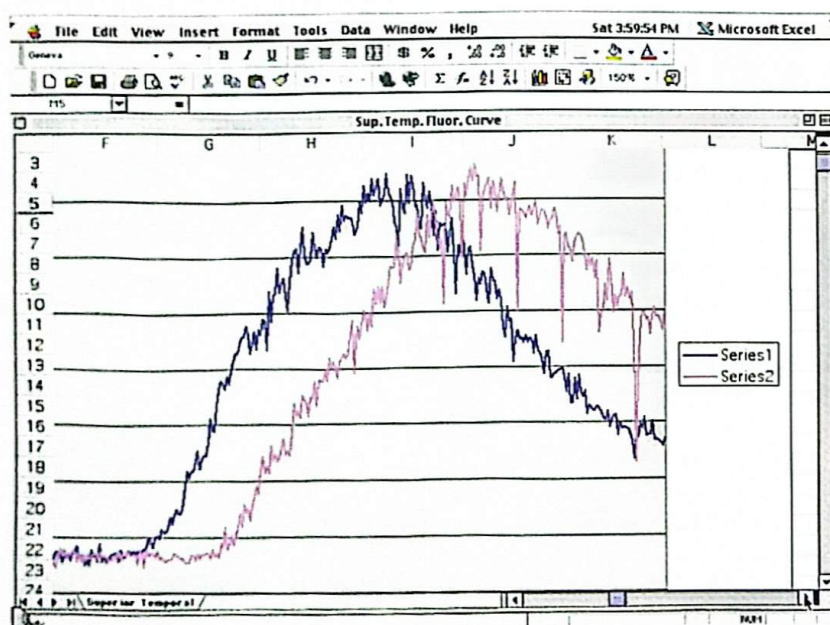


FIGURE 2.92

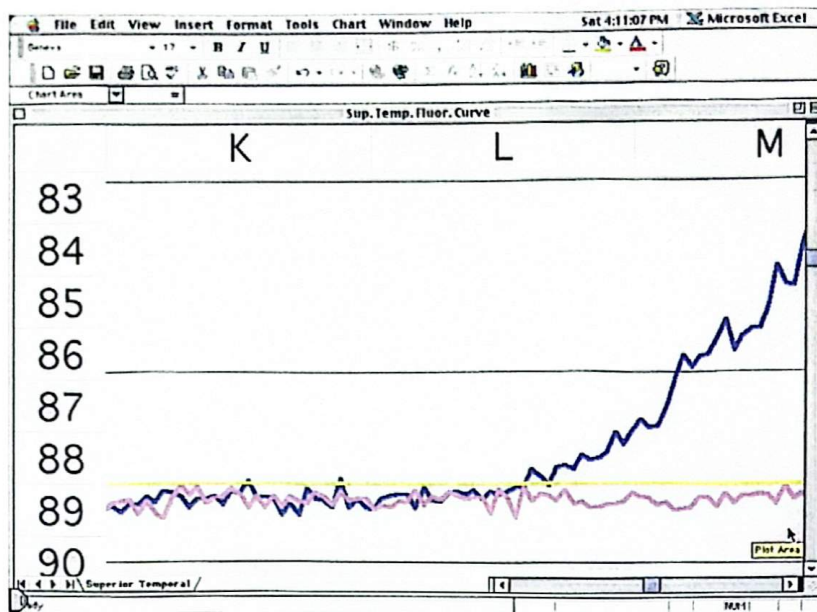


FIGURE 2.93

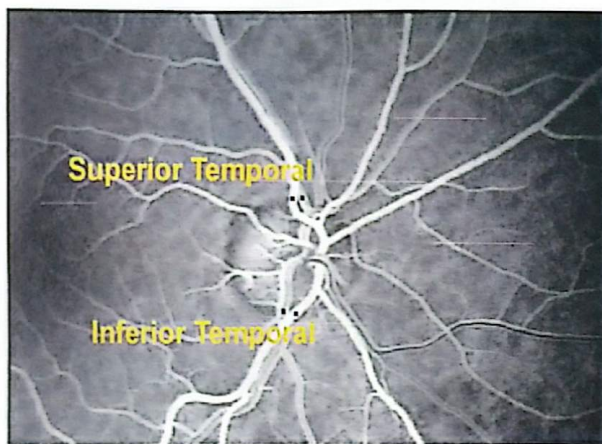


FIGURE 2.94

arrival is approximately 45 to 50 frames. A change of 10 frames, which represents only a quarter of a second, may be enough to reach statistical significance in a study. In addition, dye dilution analysis technique has the advantage of being sensitive to regional changes in retinal blood flow, as the procedure is performed on both the inferior and superior artery and vein pairs (Figure 2.95).

The greatest disadvantage of FA AVP time analysis is that it produces a measurement in seconds. Flow is measured in units of milliliters per gram of tissue per second. The amount of time required for blood to traverse the retinal vasculature may indicate some clinically relevant information concerning retinal blood flow, but this is far from the metabolic information desired. Analyzing changes in AVP time with disease may provide the most clinically relevant data. However, the magnitude of improvement in AVP time necessary to

Pros

- High resolution
- Large field (40 degree)
- Measurement of visible dye Movement
- Measurement of vessel Diameter

FIGURE 2.95

Cons

- Relatively invasive
- Pupil dilatation
- Sensitive to dye injection technique
- Analysis difficult and long (40 min)

FIGURE 2.96

induce significant improvements in retinal metabolism is unknown (Figure 2.96). Other disadvantages of the technique include its invasive nature, specifically the need for pupil dilation, and the injection of dye. Clearance of dye limits the design of clinical experiments, eliminating the use of rapidly repeated examinations.

Reproducibility data and normative data are presented in Figures 2.97 and 2.98, respectively (Wolf, Arend, Reim, 1994). The figures represent AVP time analysis before the recent additions of time-based correction and frame deinterlacing into the analysis procedure. In a different series of experiments, scleral suction was used to increase IOP. AVP and arm-to-retina times were found to be correspondingly increased (Schulte, Wolf, Arend, 1996) (Figure 2.99). Arm-to-retina time is defined by the amount of time from injection of the dye to the first appearance of dye in the eye.

Reproducibility	
Arteriovenous Passage time:	15%
Capillary Transit Velocity:	18%

FIGURE 2.97

Health and Disease	
Normal AVP:	1.58+.4 sec.
Normal arterial dye velocity:	6.67+1.6mm/s
Capillary transit velocity:	2.89+.4 sec.

FIGURE 2.98

Health & Disease II	
Normal:	IOP↑ → ART & AVP ↑
Normal:	mac. CTV < PP CTV
POAG:	AVP↑, MDV ↓
Diabetic Ret:	AVP↑
Cystoid mac. edema:	CTV↓

FIGURE 2.99

FA studies have also compared eyes affected by disease with healthy eyes. In healthy eyes, the velocity of blood in the peripapillary capillaries was greater than the velocity of blood in the perimacular capillaries. This may possibly be due to higher arterial pressure in the vessels near the disc as opposed to those in the peripheral retina. This difference was not observed in the eyes of patients with normal tension glaucoma (NTG) (Figure 2.100). Patients with NTG also presented with AVP times slower than normal. The effect of various medications on AVP time has also been studied (Figure 2.101).

Health & Disease III	
NTG:	mac. CTV = PP CTV
NTG:	Carotid to Retina time ↑
NTG:	AVP ↑
NTG w/ hemifield:	VF ↓ AVP ↑

FIGURE 2.100

Medications	
Normal:	Dorzolamide AVP ↓
Normal:	Dorzolamide Cap. Vel. ↑
NTG:	Betaxolol AVP ↔
NTG:	Dorzolamide ↑

FIGURE 2.101

SLO Resolution	
- GRDC 40 degree pixel	size: 11.6 x 13.25 micrometers
- GRDC 20 degree pixel	size: 11.6 x 13.25 micrometers
- Capillary Velocity= time/distance	

FIGURE 2.102

Exact pixel size may vary between machines, depending on performance of the rotating mirror. For example, the SLO at Indiana University has been calibrated by imaging a target with known dimensions. The pixel resolution was found to be $11.6 \times 13.25 \mu$ per pixel at 40° . By converting distance measurements on SLO images from pixels to micrometers, large vessel diameter and blood velocity measurements can be computed (Figure 2.102). In Figures 2.103 and 2.104, the macula is imaged at 20° while a bolus of dye travels through a perimacular capillary. The movement of individual dye particles is often observed in 20° perimacular and peripapillary fluorescein angiograms. The frame-to-frame distance can be measured in pixels and converted to micrometers for an absolute distance. The frame rate can be converted to a time measurement between frames; however, use of the encoded time signal to read the time difference between frames is more reliable.

As explained earlier, the CLBF uses Doppler shifts to measure velocity. Those velocities correlate significantly to blood velocity in the central retinal artery as measured by CDI. However, further validation of the CLBF's ability to accurately translate measurements of Doppler shift into velocity is difficult without a microscope flow

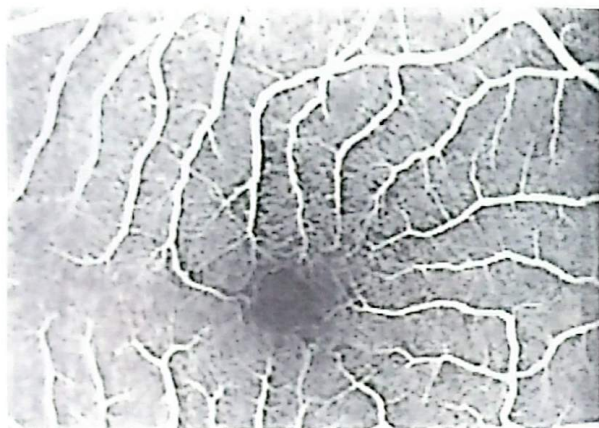


FIGURE 2.103

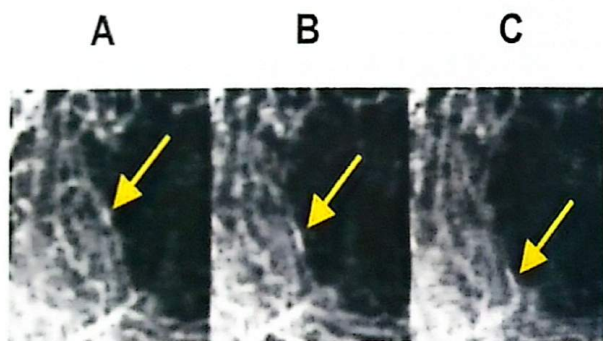


FIGURE 2.104

phantom and accurate low-flow pump. FA measurements of capillary velocity have the distinct advantage of measuring visible events, that is, the movement of dye. In addition, unlike dilution curve analysis, minimal software is required. Only one distance measurement necessary, and this may be accomplished by many commercially available software packages. Ideally, if a perfect frame grabber existed, AVP time could be calculated by counting frames. In reality, a video timer with high temporal resolution is used when recording the angiogram, and AVP times are read from sequential frames (Figure 2.105).

In reality, producing clear, sharp images of the perimacular capillary beds is difficult. In healthy individuals, angiograms of sufficient quality may be obtained in approximately 75% of the participants in a study. In patients with NTG, the figure drops to approximately 50% and is near zero in elderly patients with age-related macular degeneration (AMD), even with minimal concealment of the vessels by the disease process. Therefore capillary velocity measurements are difficult to use in glaucoma studies and nearly impossible to use in AMD studies (Figure 2.106).

Conversion of pixels to micrometers is useful in area measurements, as well as those of distance. In the case of avascular zones, accurate measurements require clear visibility of all capillaries in the perimacular region. In

Pros
- Direct measurement of visible movement of dye - Minimal analysis software necessary

FIGURE 2.105

Cons
- Difficult to obtain adequate image quality in glaucoma subjects - Nearly impossible in AMD subjects

FIGURE 2.106

such a video frame, the foveal avascular zone can be traced manually. This ability requires software that allows such image analysis; a large, high-quality computer monitor; and a steady hand on the mouse. If a large amount of computer tracing work is anticipated, a computer graphics pad is superior to a mouse and is worth the investment. Previous studies have found that the size of the foveal avascular zone is increased in patients with diabetic retinopathy and acquired immunodeficiency syndrome (Figure 2.107).

The HRA (HRA, Heidelberg Engineering, GmbH, Heidelberg Germany) system is a completely digital SLO that also can produce fundus angiograms. Instead of recording a video sequence onto a Super VHS tape, each frame of it is stored individually on the HRA hard drive. The number of frames that can be acquired is limited by the memory of the HRA computer. The total length of any individual segment is therefore limited to a short amount of time (1 to 2 minutes at full frame rates) before recording must stop and frames are saved to the hard drive (Figure 2.108).

The HRA requires less skill on the patient's part than SLO. The examined eye gazes into the camera. However, unlike the Rodenstock SLO, the HRA can be

moved to locate and frame the desired anatomy. The patient is instructed to focus on a distant stationary target with the fellow eye, and the HRA camera head is positioned to frame the area of interest on the fundus (Figure 2.109). The levels of laser light intensities are similar in the SLO and HRA.

The HRA is more sensitive to small head movements than the SLO. While undergoing SLO, a patient could drift away from the headrest without the technician being aware. This slight movement makes it challenging for the technician to center and focus the image, but it can occur without a noticeable change in image quality. Should the patient's head drift away from the forehead bar while undergoing HRA, the near complete loss of the image is immediately evident (Figure 2.110).

At 20 frames per second, 1,200 images are generated each minute. Each image contains 65,536 individual pixels, each representing the fluorescence detected at a $30 \times 30 \mu\text{m}$ area of the fundus (Figure 2.111). At its highest frame rate, a 1-minute angiogram segment

Health and Disease

- Foveal avascular zone size is increased in AIDS, and diabetic retinopathy (dr) patients
- Capillary blood velocity is reduced in dr

FIGURE 2.107



FIGURE 2.108



FIGURE 2.109

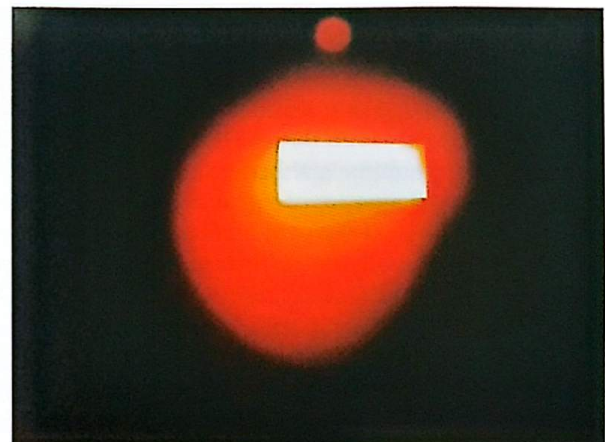


FIGURE 2.110

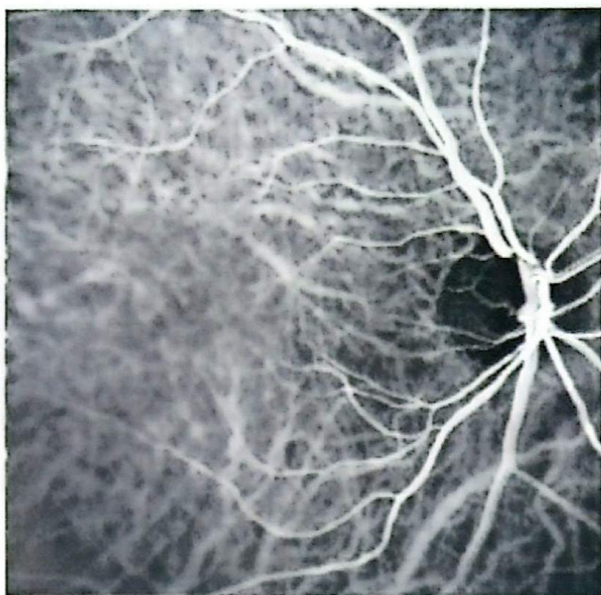


FIGURE 2.111

requires 75 MB of hard drive space for storage. Of course, the machine must also have 75MB of available RAM to even record such a sequence (Figure 2.112).

Backing up data is crucial in a busy clinic; without diligent backup, the computer hard drive memory will be used up very quickly. Consider the filling phase of an FA and the filling phase of an ICG angiogram. Assume that only the first minute is necessary to capture dye entering the eye. This would produce two 1-minute segments. In a busy research clinic, it is easily possible to perform ten examinations in a day. The total data generated (remember just the filling phase) would be 1.5 GB. Until recently, that would have been too much data for a single hard drive. Personal computer (PC) technology is only now catching up to the space demands of digital imaging systems (Figure 2.113).

The greatest advantage of the HRA is that the images produced are digital. Rodenstock SLO data begins as a voltage level that is digitized within the SLO imaging system. This digital level is converted back to analog to form the video signal out of the machine. The signal is stored in analog format on the S-VHS tape and converted back to digital by a frame grabber for analysis. In each of these steps, a small amount of signal degradation occurs. In the case of HRA, no digitization is required for computer analysis of angiograms. Images are, and remain in, their original state (Figure 2.114).

As opposed to the SLO, HRA has several disadvantages. HRA images are of a lower spatial and temporal resolution than SLO images. SLO produces a video signal using National Television Standards Committee (NTSC) standard, used in the United States, and Phase Alternating Line (PAL), standard in most of the rest

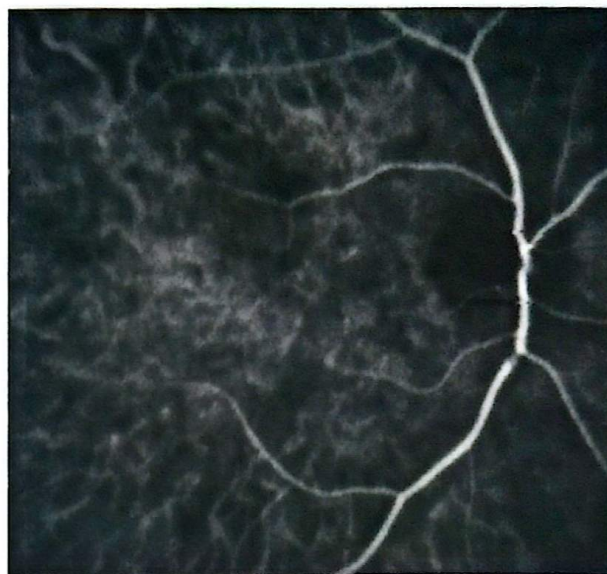


FIGURE 2.112

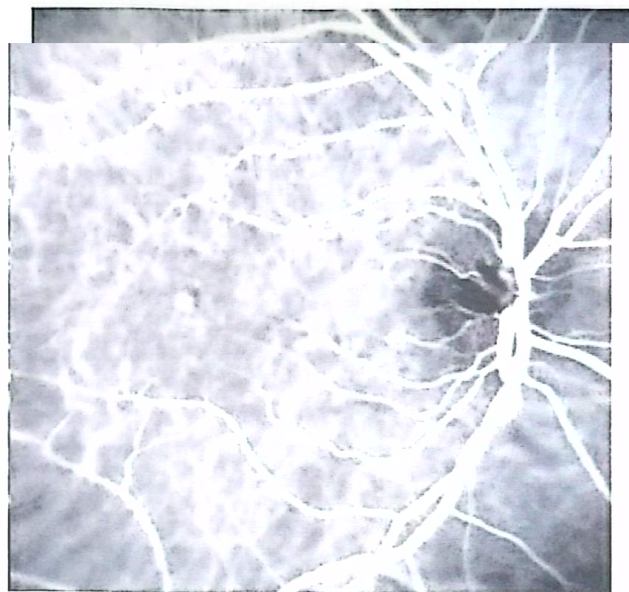


FIGURE 2.113

of the known world. The conventional NTSC standard image contains 525×427 pixels, as opposed to the 256×256 pixel 20 frame per second (fps), or 512×512 pixel 10 fps HRA image sequence. Further, the NTSC standard video signal displays images at 30 per second, and the maximum HRA temporal resolution is 20 frames per second. Of course, at maximum resolution, the HRA cannot record long segments of digital video (Figure 2.115). The other disadvantage of the HRA is its sensitivity to small head movements, making patient compliance vital.

Pros
- Digital system preserves image quality - No data loss during digitization for analysis

FIGURE 2.114

Cons
- Lower resolution than Rodenstock SLO 256 x 256 pixels - Small head or eye movements destroy the image

FIGURE 2.115

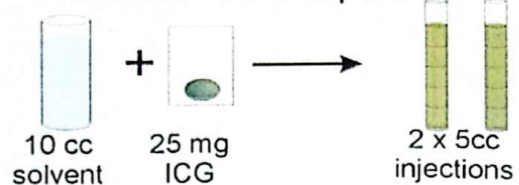


FIGURE 2.116

INDOCYANINE ANGIOGRAPHY FOR ANALYSIS OF CHOROIDAL HEMODYNAMICS

Indocyanine green (ICG) angiography can be performed on either a Rodenstock SLO 101 (Figure 2.116) or the HRA digital SLO. To quantify the ICG angiogram, the Glaucoma Research and Diagnostic Center (GRDC) uses a small injection of high-concentration ICG dye. One cubic centimeter of solution contains the same 12.5 mg of dye used in the standard clinical dosage (Figure 2.117).

Clinical ICG Preparation



GRDC ICG Preparation

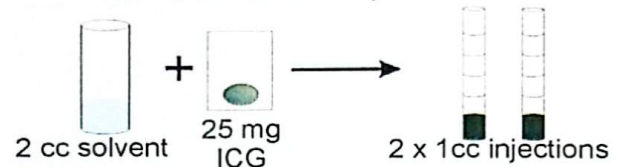


FIGURE 2.117

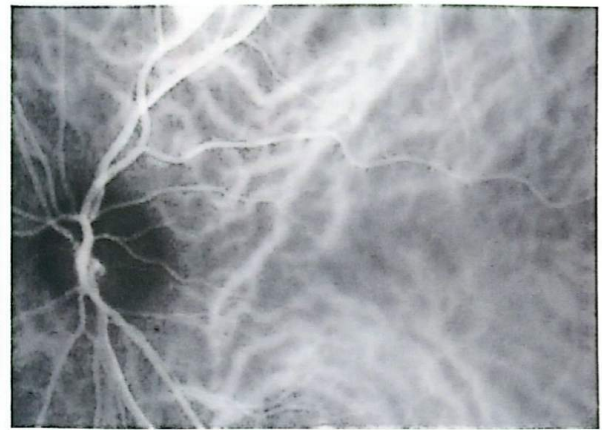


FIGURE 2.118

This concentration allows rapid injection of a small bolus of dye. Previous work using the standard 5-cc injection produced prolonged dye filling curves with indistinct features. The smaller 1-cc bolus contains the same amount of fluorescent material; however, the smaller volume facilitates rapid entrance into and clearance from the eye (Figure 2.118). To graph angiogram intensity, it is also important that the image never saturate, that is, the amount of fluorescent light does not exceed the sensitivity of the instrument's photodetector. The GRDC therefore uses laser and photodetector sensitivity settings that result in darker images than those obtained in the normal clinical examination.

The series of Figures 2.119 through 2.124 shows the filling and clearance of ICG in an SLO angiogram. This image series was obtained on a Rodenstock SLO 101. In Figure 2.119, dye is just beginning to arrive in the fundus. Note that dye arrival is more rapid in the perimacular region, and the peripapillary area remains relatively dark (Figure 2.120). This difference in areas becomes more evident, and quantifiable, when area



FIGURE 2.119

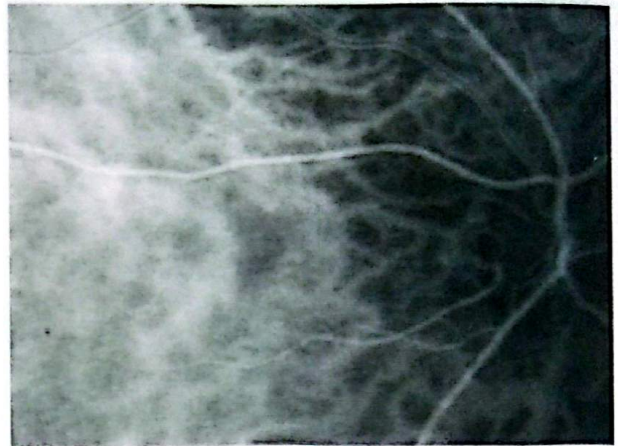


FIGURE 2.121

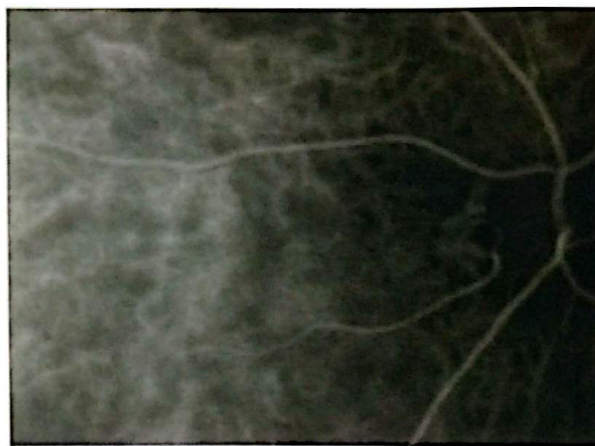


FIGURE 2.120

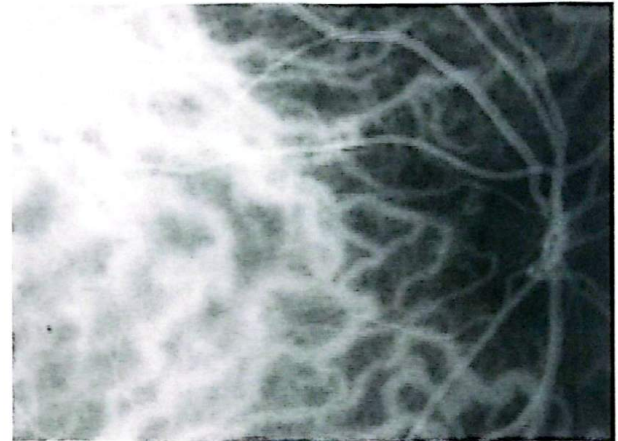


FIGURE 2.122

dilution analysis is performed. To quantify this video series, fluorescence levels in four areas surrounding the macula and two areas temporal to the disc are graphed. The high level of brightness in the macular region is due, in part, to the higher density of large choroidal arteries in the area (Figure 2.121). Maximum brightness is observed as the dye is distributed throughout the choroidal arteries and veins (Figure 2.122) before large amounts of dye have cleared from the choroid (Figure 2.123). The dye leaves the eye through the choroidal venous system (Figure 2.124).

The same examination may be performed by HRA. The HRA control panel (Figure 2.125) differs from that of the HRF and HRT in appearance. The control panel can be used to adjust laser intensity, gain the field of view, and focus the image. As with HRA FA, the same difficulties in sensitivity to movement are encountered with ICG image acquisition (Figure 2.126).

Figures 2.127 through 2.132 present a series of ICG angiogram frames obtained on the HRA. As with FA, HRA



FIGURE 2.123

provides a lower resolution image, only 256×256 pixels compared with the 525×427 pixels of the NTSC video signal and the 640×480 pixels produced by the frame grabber. HRA does produce sharper images of the fundus,

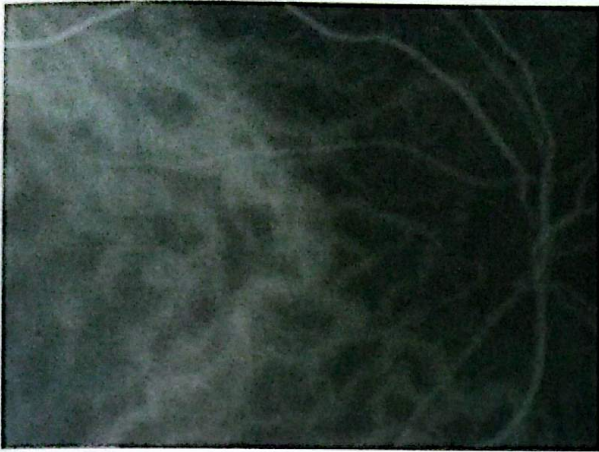


FIGURE 2.124



FIGURE 2.125

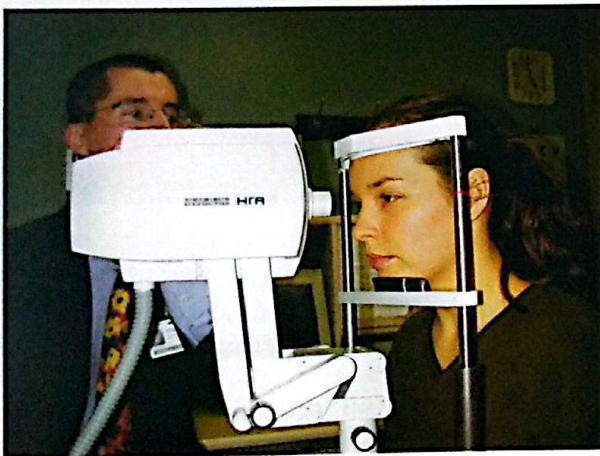


FIGURE 2.126

and these images are collected and stored in a digital format, making them immune to data degradation associated with aging videotape. Again, because of the large amount of data produced by a digital angiogram,

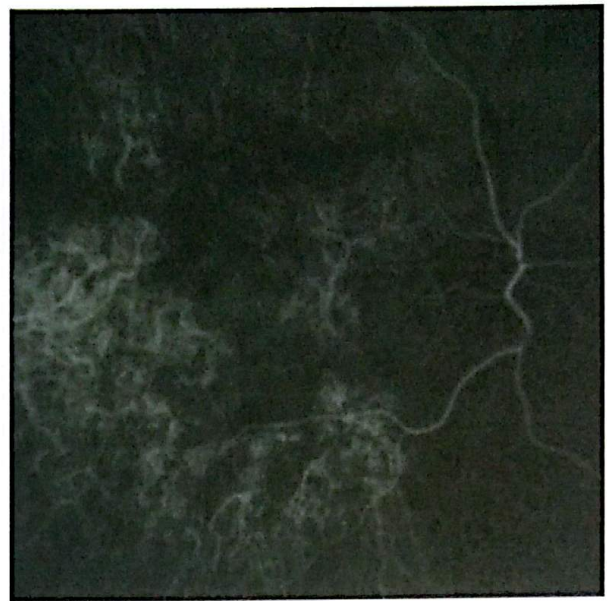


FIGURE 2.127

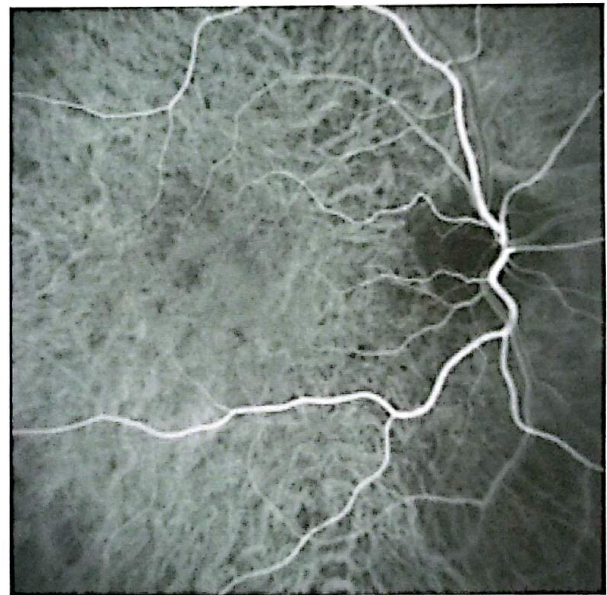


FIGURE 2.128

HRA data must be archived frequently, which is not a problem encountered with S-VHS video recording of SLO angiograms.

To demonstrate the creation of a dye dilution curve, the average brightness in an arbitrary area of interest will be graphed from each of the video frames in Figures 2.127 through 2.132. The graphs are displayed in Figures 2.133 through 2.138. The fluorescence level within a superior temporal peripapillary sample window that is positioned on the first frame is measured and graphed. With repeated sampling of a single tissue location within frames throughout the

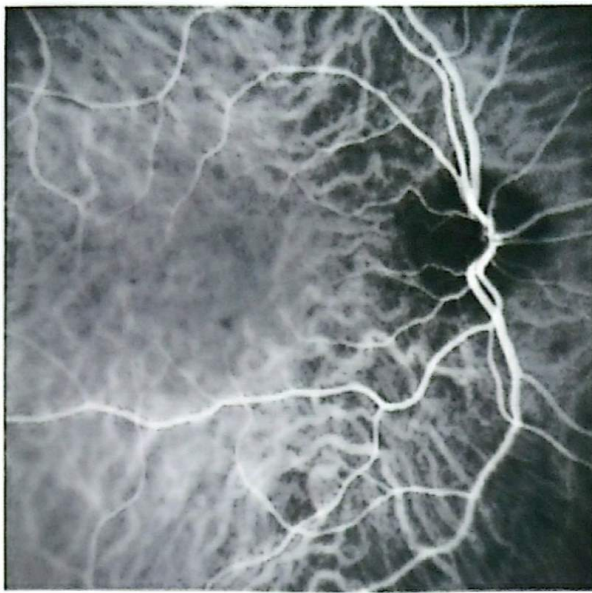


FIGURE 2.129

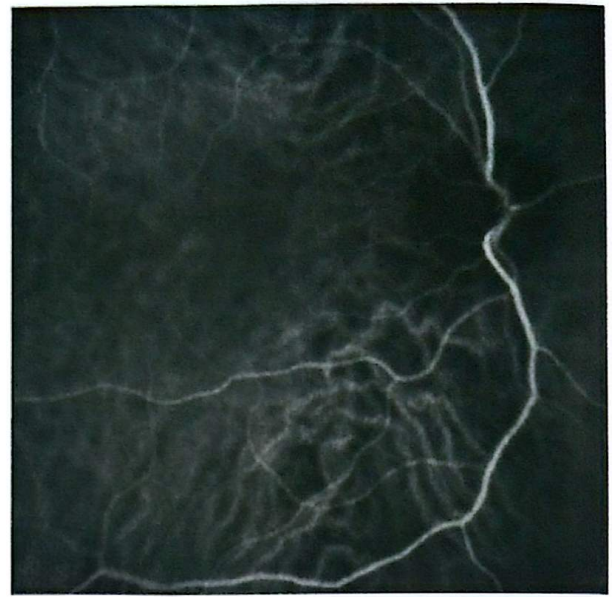


FIGURE 2.131

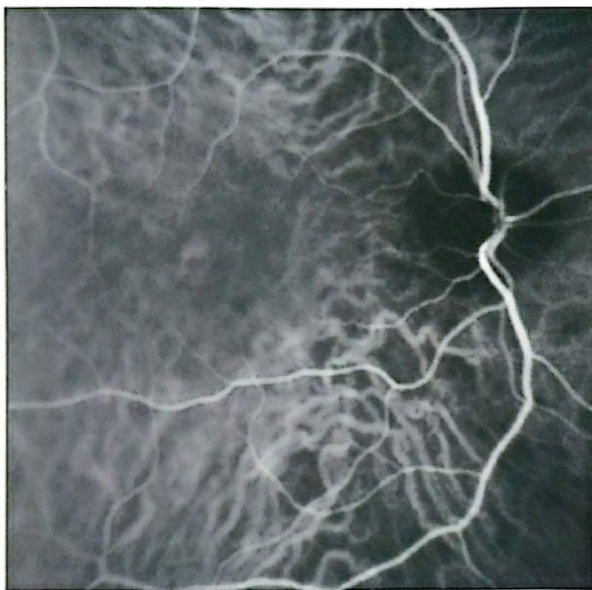


FIGURE 2.130

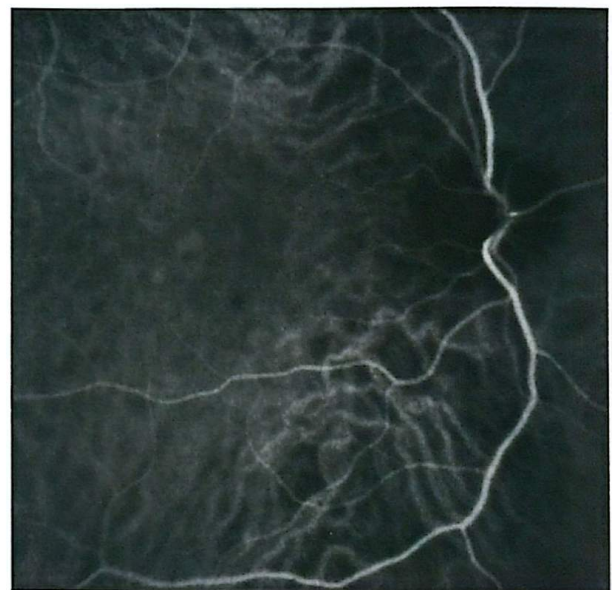


FIGURE 2.132

filling cycle, a dye dilution curve is constructed. As data accumulates, the characteristic filling curve becomes evident. In this sequence, the fourth measurement (Figure 2.136) in this dilution curve confirms that dye clearance is underway. Despite the apparent darkness of the image, the fluorescence level remains well above the predye baseline level as dye begins to recirculate (Figure 2.138). These six graphs represent only 2% of the total data contained in just one dilution graph. To calculate the parameters used in area dilution analysis, this sampling and graphing process is performed 1,800 times. Figure 2.139 maps the six areas from which

dye dilution graphs are constructed: four surrounding the macula (*B*, *C*, *E*, and *F*), and two near the disc (*A* and *D*).

The dilution curves are first analyzed individually, and then comparisons of several parameters are made between curves (Figure 2.140). The filling slope, representing the rate of dye filling, is calculated for each curve independently (Figure 2.141). The 10% time describes the dye arrival times at the various areas measured. It is defined as the amount of time between dye injection and the achievement of 10% of total brightness above baseline (Figure 2.142). The 63% filling time is

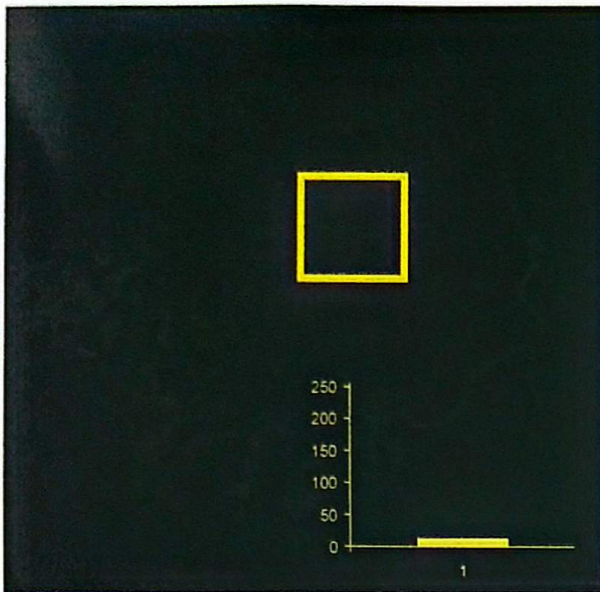


FIGURE 2.133

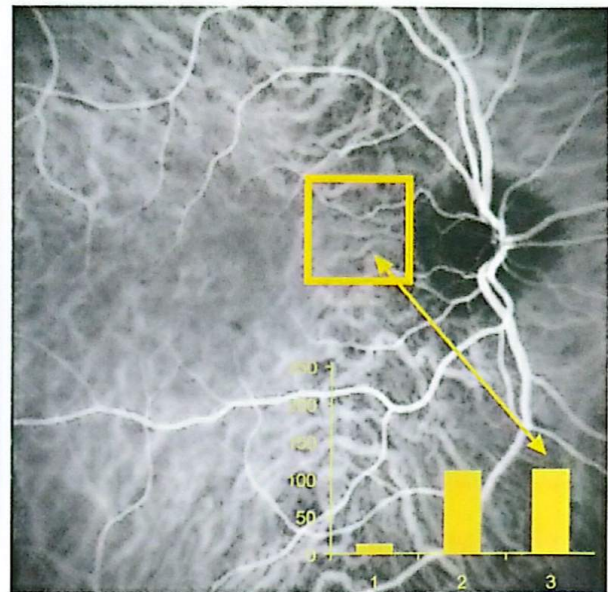


FIGURE 2.135

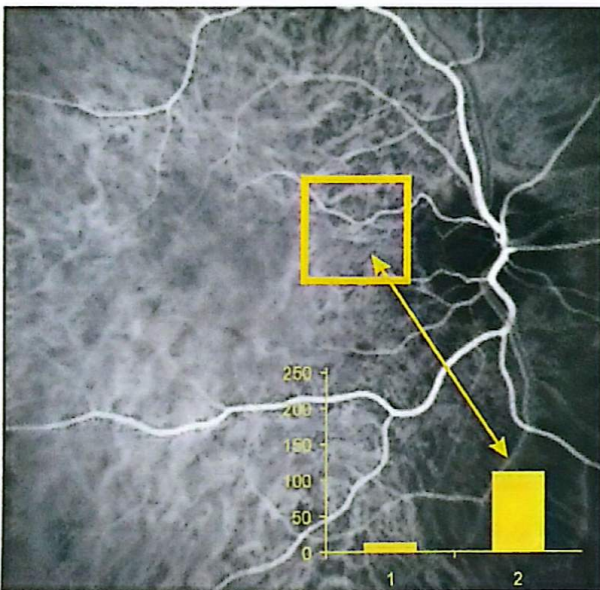


FIGURE 2.134

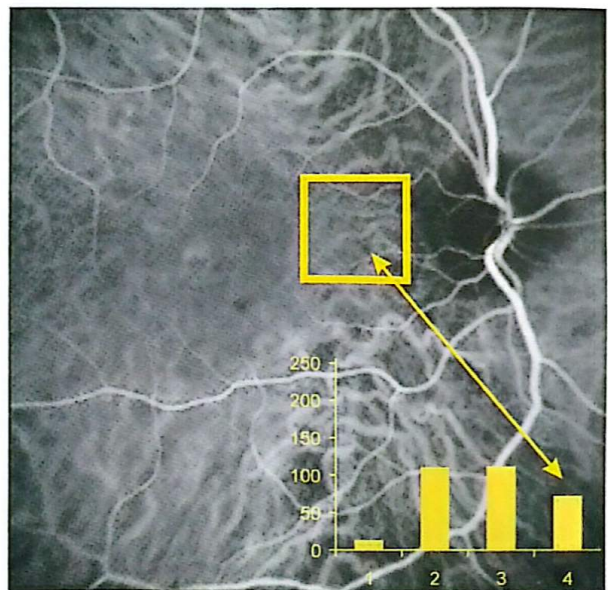


FIGURE 2.136

influenced by both dye arrival and the filling rate of the different areas. Dye duration in the choroid is quantified by measuring the width of the curves and represents the amount of time that dye lingers in the choroid (Figure 2.143). Faster flow rates will have smaller dye duration times. The difference between macular and peripapillary 10% times can be used to quantify the rate of dye passage through the choroidal vasculature (Figures 2.144, 2.145). Similarly, the difference in macular and peripapillary maximum brightness level quantifies the difference in vascular density between the two regions (Figure 2.146).

The greatest advantage of ICG angiography is that data is gained directly from the choroidal vasculature. Furthermore, regional information comparing one area to another is produced (Figure 2.147). Parametric analysis of the angiograms requires an expensive digital video analysis system, customized software, and approximately 45 minutes per data point (Figure 2.148). This technique is by no means practical in a clinical environment; however, useful knowledge of multiple diseases, such as glaucoma and AMD, is being gained through digital analysis of ICG SLO angiograms in an academic research setting. The use of ICG angiography could also

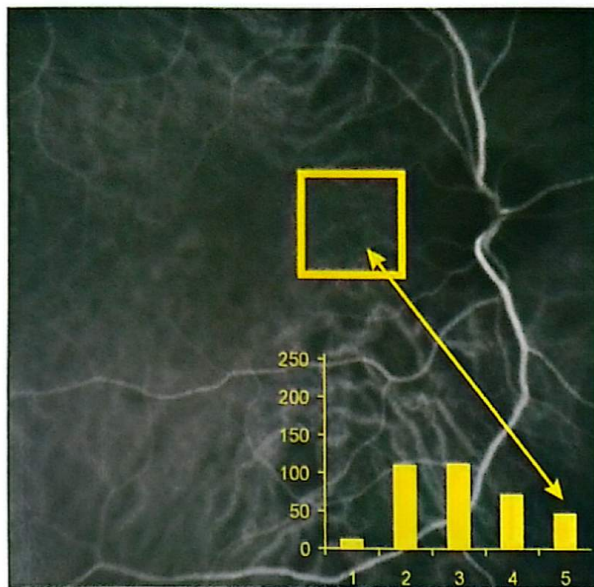


FIGURE 2.137

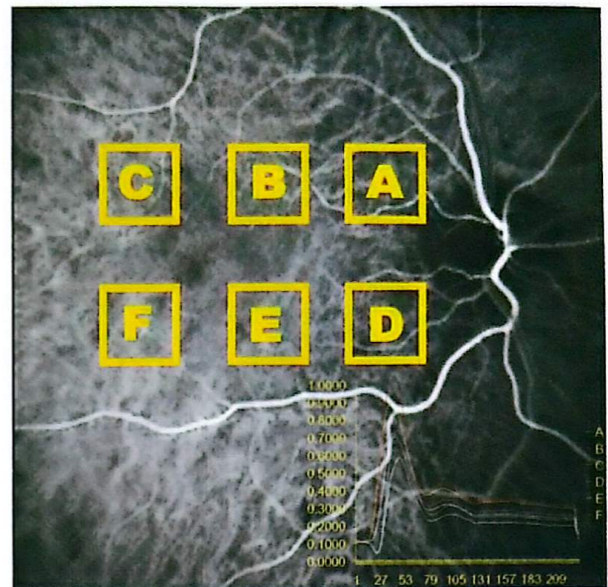


FIGURE 2.139

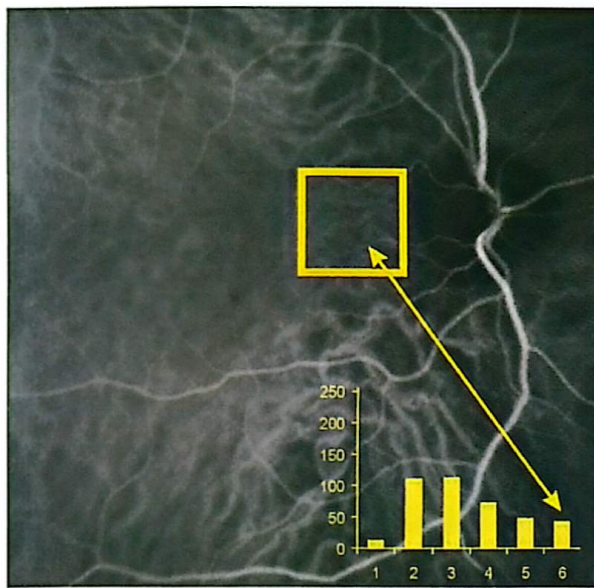


FIGURE 2.138

be extended to provide information on arteritic and non-arteritic anterior optic neuropathies amongst other conditions.

Reproducibility of the technique varies between parameters. However, with a coefficient of variation of approximately 18% for most, this variability has been found to be acceptable (Figure 2.149). Subjects with NTG have greater delays in peripapillary choroidal filling compared with age-matched controls. This may suggest sluggish movement of dye through the

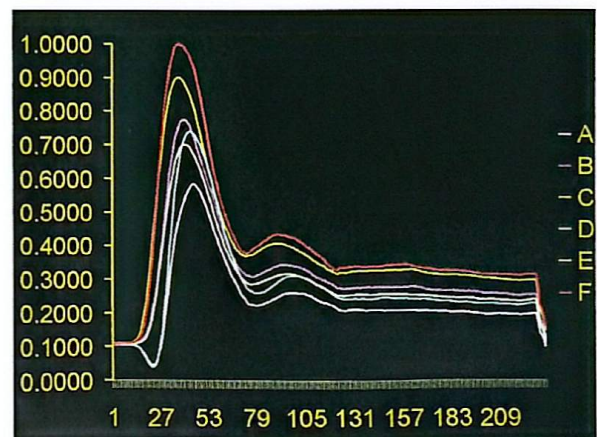


FIGURE 2.140

choroidal vasculature of NTG subjects. AMD subjects present with delayed 10% and 63% macular choroidal filling times compared with age-matched controls (Figure 2.150). Validation is important with any new analysis technique. Figure 2.151 shows the correlation of filling delays observed in the choroid by area dilution analysis and resistance to flow in the choroid as measured in the nasal posterior ciliary arteries. As choroidal resistance to flow increases, the delay in peripapillary filling, shown by slow movement of dye across the choroid, is increased (Figure 2.151). Further validation is required; however, early data obtained from the choroid agrees with other measurements obtained from the surrounding vasculature.

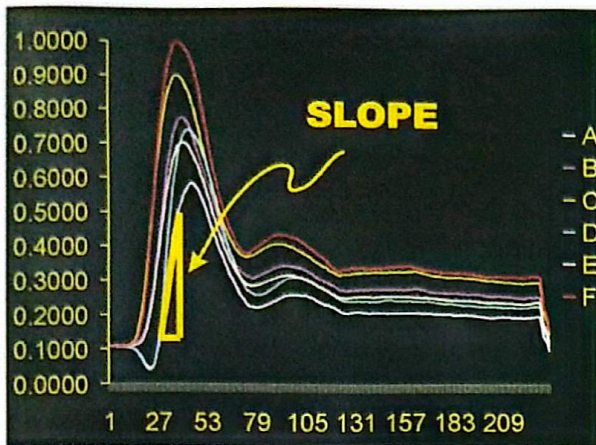


FIGURE 2.141

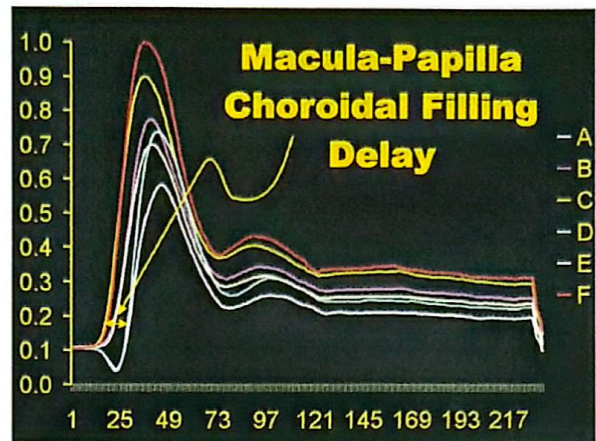


FIGURE 2.144

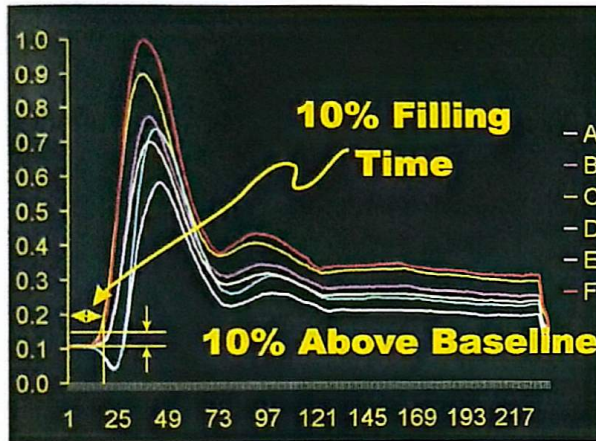


FIGURE 2.142

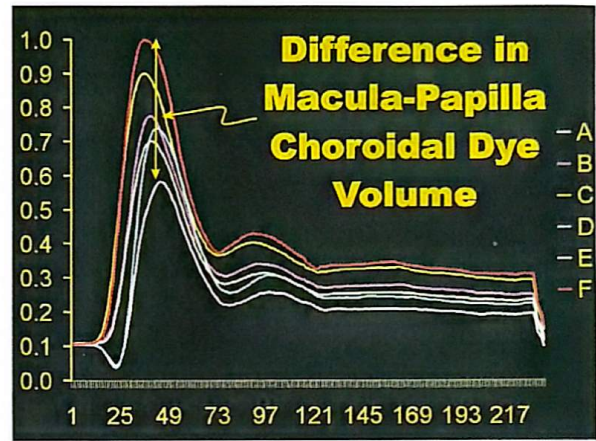


FIGURE 2.145

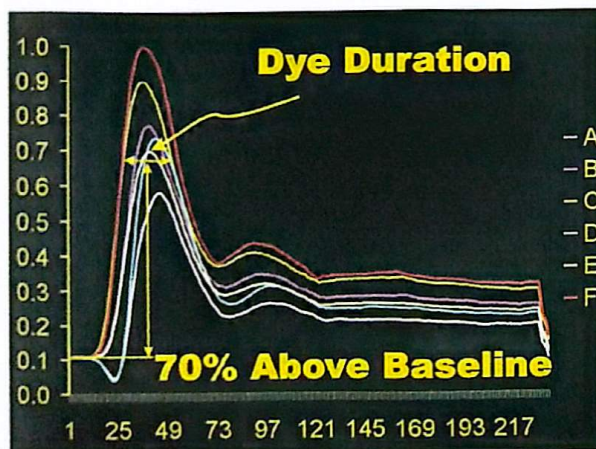


FIGURE 2.143

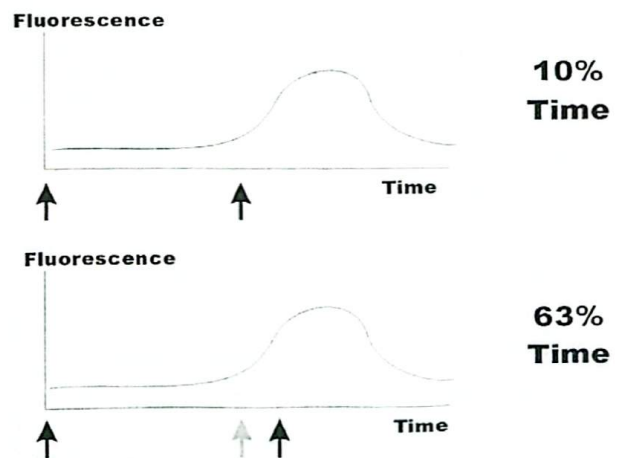


FIGURE 2.146

Pros

- Visible individual choroidal vessel
- Hemodynamic data in addition to morphological information

FIGURE 2.147

Cons

- Relatively invasive pupil dilation
- Sensitive to dye injection technique
- Fast & precise alignment program is required
- Analysis is difficult and time Consuming (40 min.).

FIGURE 2.148

Cons

- Relatively invasive pupil dilation
- Sensitive to dye injection technique
- Fast & precise alignment program is required
- Analysis is difficult and time Consuming (40 min.).

FIGURE 2.149

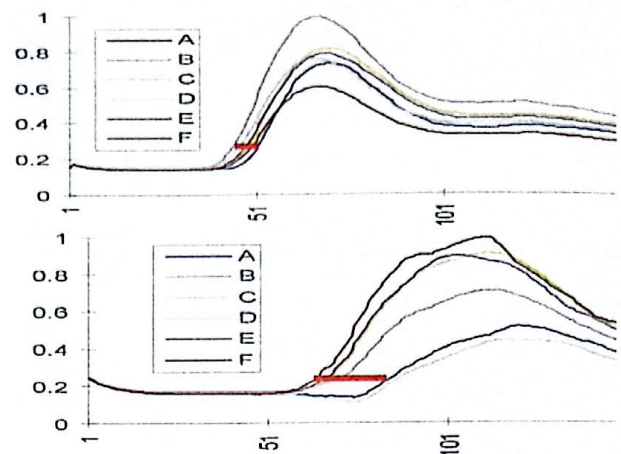


FIGURE 2.150

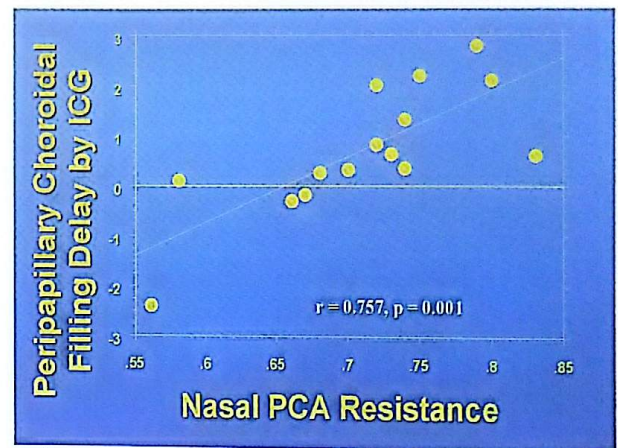


FIGURE 2.151

Laser Doppler Flowmetry

LASER DOPPLER FLOWMETER

The Laser Doppler Flowmeter (LDF) (Oculix LDF Philadelphia, PA. USA) is a laser Doppler device consisting of a modified fundus camera and computer. Unlike the CLBF, the LDF is not designed to examine velocity in large vessels, but volumetric flow in the capillary beds of retinal tissue. Although no longer commercially available, the device is well represented in the medical literature (Figure 2.152).

A laser is focused onto a 50- μ m diameter circular area of the fundus. Research published in the *American Journal of Ophthalmology* found that the flow measurement could not distinguish retinal or choroidal sources of Doppler shifts (Petrig BL, Riva CE, Heyreh SS, 1999).



FIGURE 2.152

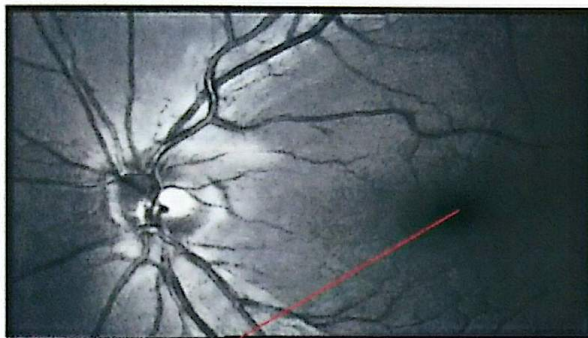


FIGURE 2.153

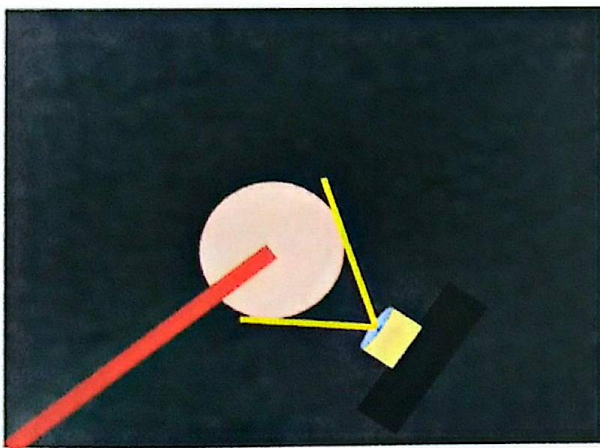


FIGURE 2.154

Therefore LDF is now primarily used to measure choroidal blood flow in the foveal avascular zone (Figure 2.153). Although the measurement of choroidal flow within the avascular perimacular region may consist

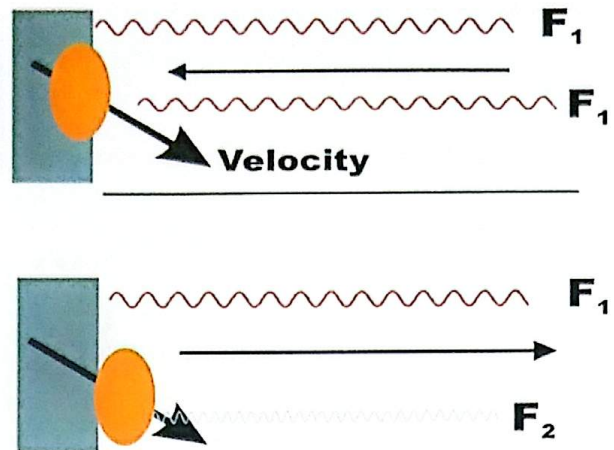


FIGURE 2.155

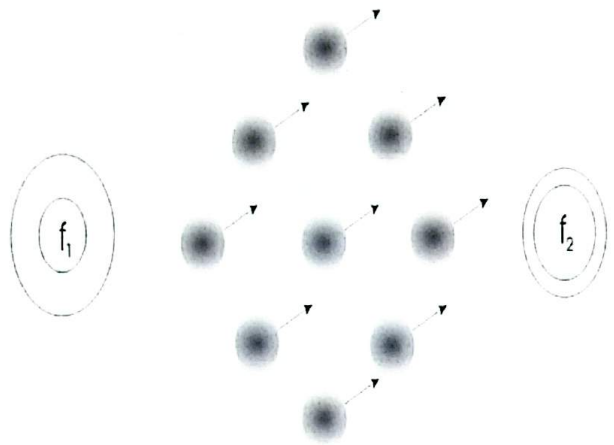


FIGURE 2.156

primarily of Doppler shifts originating in the choroidal vasculature, the measured tissue area represents only a minute percentage of the entire choroid.

A photodetector collects scattered light from a 150- μm circular area of the fundus surrounding the laser spot (Figure 2.154). By including an area larger than the incident beam, laser light can scatter deeply into the tissue being measured. In general, the greater the separation between the incident beam and the detector, the deeper the sources of Doppler shifts within the tissue.

The photodetector will receive Doppler-shifted light as well as non-Doppler-shifted light (Figure 2.155). These multiple frequencies interfere with each other, forming a drifting pattern of nodes as seen with the laser Doppler velocimeter and Canon Laser Blood Flowmeter (Figure 2.156). As with the other laser Doppler technologies, the photodetector in the LDF analyzes the beat frequency of the interference pattern.

Pros
- Volumetric flow measurement - Signal from capillary beds

FIGURE 2.157

Cons
- 50 micrometer laser spot can hit or miss hidden choroidal vessels. - Unknown retinal contribution away from macula. - Flow in arbitrary units.

FIGURE 2.158

The LDF has the advantage of producing localized volumetric flow measurements from capillary beds within the fundus (Figure 2.157). In its day, it was a state-of-the-art hemodynamic analysis device.

The disadvantages of the LDF are plentiful. The main one is that meaningful data is limited to choroidal measurements obtained only through the foveal avascular window. Measurements obtained anywhere else in the fundus would include some unknown blend of retinal and choroidal blood flow (Figure 2.158). The ratio of choroidal to retinal blood flow varies with location and is unknown. Because the optical system is not confocal, and, therefore, is not retrieving data from a specific planar depth (as is done in SLO), separating data from multiple layers of tissue cannot be done. Consequently, it can be argued that flow data from vascular beds deep to the retina, such as the choroid, are inherently present in every LDF reading.

The LDF acquires the least reproducible blood flow measurements of any technique currently described in the literature (Figure 2.159). LDF has found peripapillary rim flow to be lower in the temporal than the nasal rim. It has also been used to show that blood flow is maintained through slow changes in IOP; however, rapid changes in IOP reduce blood flow (Figure 2.160).

Reproducibility
- Intrasession SD flow: 24% - Intersession SD flow: 32%

FIGURE 2.159

Cons
- Nasal peripapillary rim blood flow is greater than temporal peripapillary blood flow - Blood flow remains constant through slow changes in IOP, but not through rapid changes

FIGURE 2.160



FIGURE 2.161

HEIDELBERG RETINA FLOWMETER

The Heidelberg Retina Flowmeter (HRF) (HRE; Heidelberg Engineering, GmbH, Heidelberg Germany) is a confocal scanning version of the LDF. The system consists of a camera head and a computer system (Figure 2.161). Unlike the stationary laser point of the LDF and CLBF, the HRF laser quickly scans the fundus (Figure 2.162). Each scan line is divided into 256 individual points (Figure

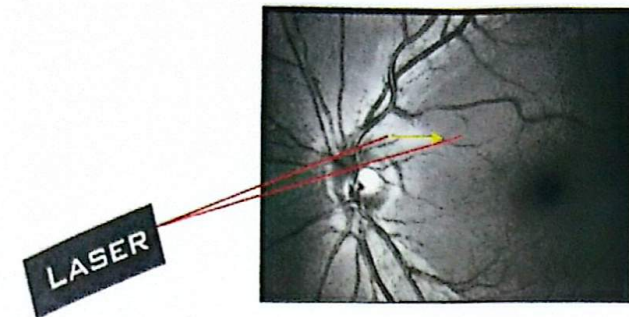


FIGURE 2.162

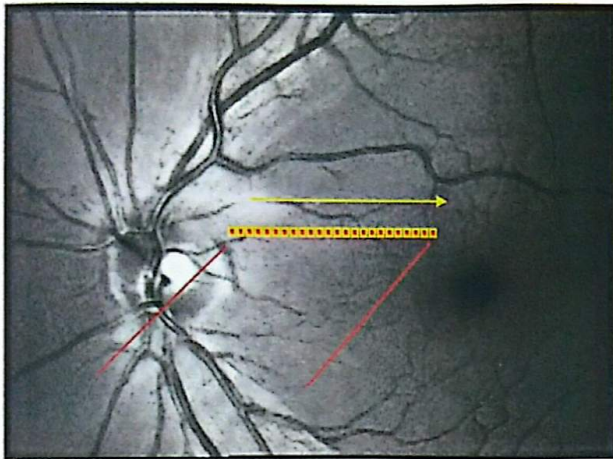


FIGURE 2.163

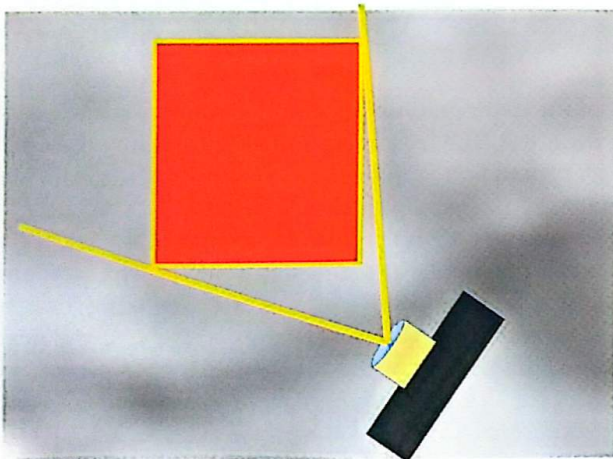


FIGURE 2.164

2.163). Doppler shifts from each point are considered independently (Figure 2.164). Scattered light from each point is quantified as with LDF; however, only scattered light from the point of illumination is analyzed by the HRF. Because separation of the incident beam and detection point, as used in the LDF (see Figure 2.154),

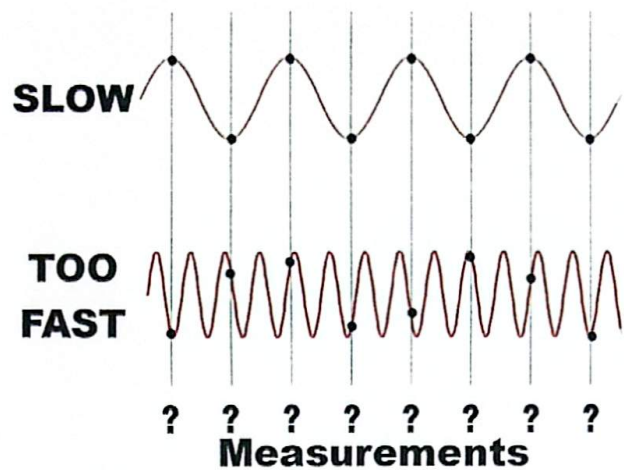


FIGURE 2.165

COMPUTER RECONSTRUCTION

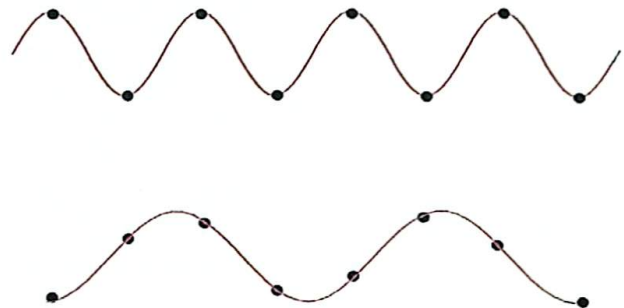


FIGURE 2.166

increases penetration of the measurement, HRF measurements tend to be concentrated on surface vasculature. In addition, the system is confocal, with a focal plane thickness of 400 μm , further eliminating the contribution of deeper tissue to the measurement.

As the HRF laser repeatedly sweeps the fundus, every point on the scanned line is measured once per scan. The effect is similar to the rotating beacon at an airport. The light is on continuously, but a motionless observer sees the light only briefly once per cycle. Every point is illuminated and sampled 128 times at a frequency of 4,000 hertz. The sampling rate limits the beat frequency that the technique can detect. The black lines in Figure 2.165 represent the moment when the two waveforms are sampled. The black dots are the measurements. One of the waveforms has a very high frequency relative to the sampling rate. When the samples are isolated and waves are reconstructed to fit the samples, the faster original wave is misrepresented by the reconstruction (Figure 2.166). Notice that the "very fast" wave is grossly distorted

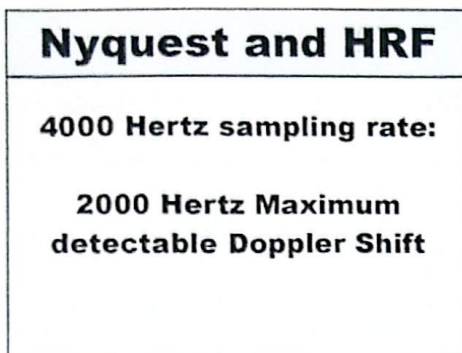


FIGURE 2.167

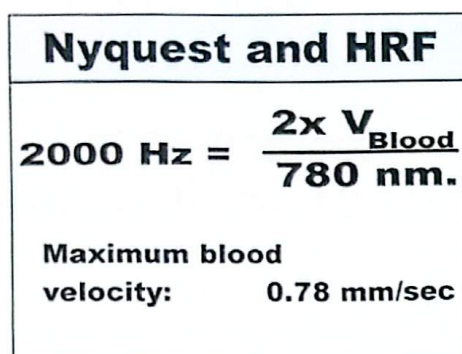


FIGURE 2.168

after reconstruction based on the samples. This is because the sample rate was too slow to obtain an accurate description of the fast wave.

As determined by an engineer named Nyquist, the digital samples must be obtained at least twice per wave to reconstruct adequately the wave from the samples (Figure 2.167). With HRF samples at 4,000 hertz, the "Nyquist frequency," or maximum measurable wave, for the HRF is 2,000 hertz. Inserting the maximum detectable Doppler shift frequency of 2,000 hertz into the Doppler equation, we see that the maximum velocity that the HRF can measure accurately is 0.78 mm/sec (Figure 2.168). FA has measured blood velocities within the perimacular capillaries at approximately 3 mm/sec. Notice that the cosine term has been disregarded in the calculation. The relative angle between the incident beam and velocity vector may allow the HRF to accurately detect change in retinal capillaries despite the limitation of the Nyquist frequency.

The database associates image data with patient information (Figure 2.173). Because the HRF software does not have a feature that backs up the database, it is vital to back up the database frequently. However, the file containing the image contains no patient demographic data. The file name of the image, which contains a reference to the database number, is the only link to

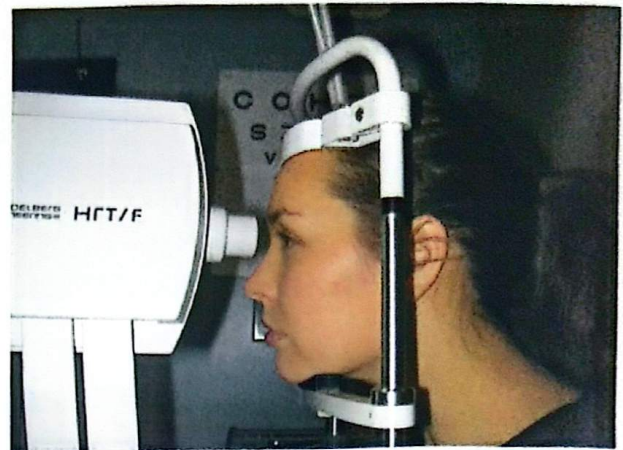


FIGURE 2.169

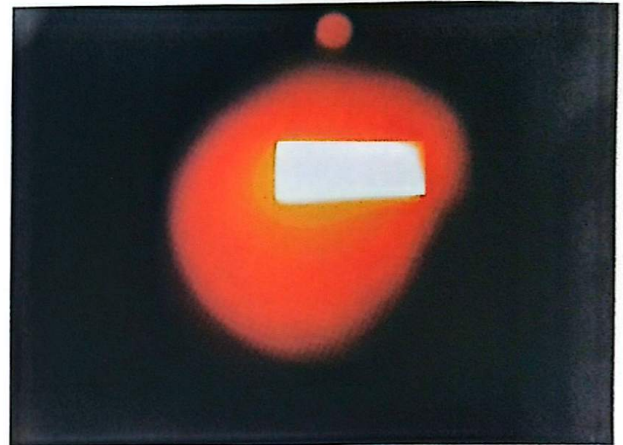


FIGURE 2.170

all of the demographic information that gives the image its meaning. The user is responsible for using the operating system software of the HRF computer to copy the database to a backup device.

Use of the HRF is very similar to that of the HRA. The patient's head is held comfortably in the chin rest and against a forehead bar (Figure 2.169). Looking into the HRF camera, the patient sees the red light of the near-infrared laser (Figure 2.170). The patient's fellow eye focuses on a distant target to avoid eye movement (note the eye chart on the far wall in Figure 2.161). The technician cannot see the laser spot on the patient's eye and therefore must adjust the camera position to align it with the eye while observing the image on the computer monitor. The optimal distance between the camera and eye is approximately 15 mm (Figure 2.171), and extreme care must be taken when working this closely to avoid contact with the eye.

The control box is used to set sensitivity (or gain), scan size, and focus (Figure 2.172). The gain setting is determined visually by the color content of the image, which should contain no white pixels.



FIGURE 2.171

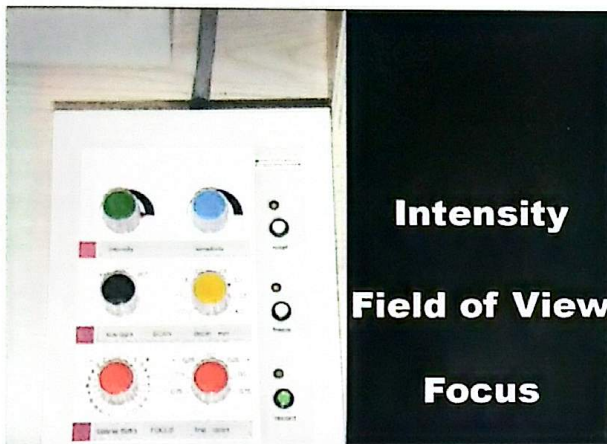


FIGURE 2.172

After a scan is complete, all raw data is displayed. Each line is scanned 128 times, and each reflectance scan is stacked. The upper left portion of the image in Figure 2.174 is the data obtained from a single scan line of the retina. Reflected light from each of the 128 scans is presented, resulting in an image that appears as vertical bars. The x-axis of the image contains data from a single line, and each line on the y-axis is a separate scan. After the frequency content of each point is determined by a Fourier transformation, it is displayed as Doppler shift intensity (Figure 2.175). The top image in the series is reflected light. The other images are representations of Doppler shifts. Just as Doppler weather radar can map a storm system by plotting air movement without ever "seeing" the clouds, the HRF can map blood flow without actually seeing or displaying blood vessels. Rather, it creates an image based on the differences in Doppler shifts between stationary points such as cells that make up blood vessels and dynamic points such as moving red blood cells.

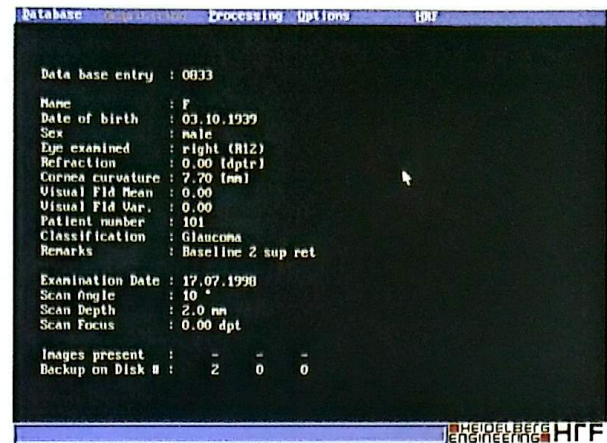


FIGURE 2.173

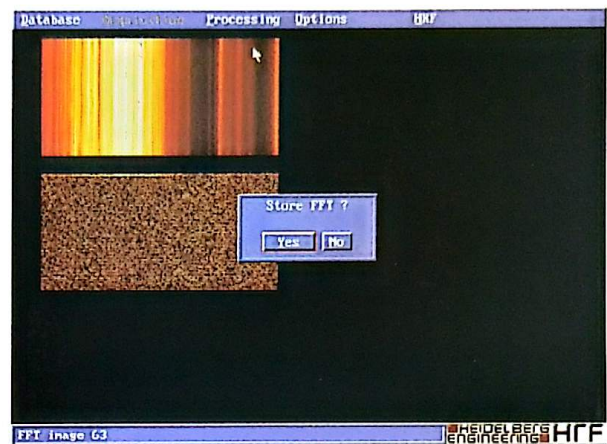


FIGURE 2.174

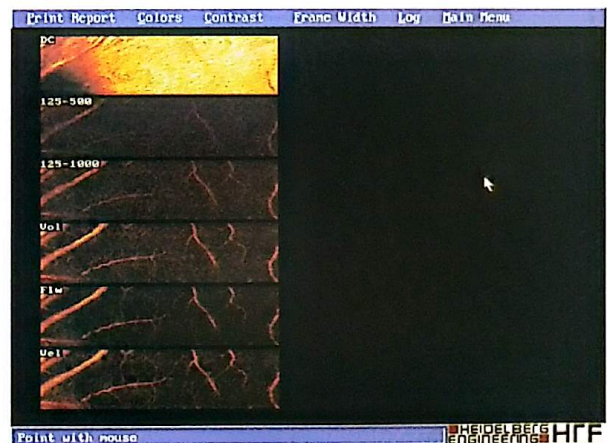


FIGURE 2.175

Use of a 40×40 sample box is a quick, convenient way to quantify image brightness in areas that are being considered for flow analysis. In the area of interest in Figure 2.176, the peripapillary retina, the image has an average brightness of 178 on a scale from 0 to 255.



FIGURE 2.176



FIGURE 2.178



FIGURE 2.177

Brightness below 70 and above 200 on the scale renders the image unsuitable for analysis. However, the overall quality of the image is still important because overly bright areas can affect measurements across the whole image. In order to visualize the vessels within the HRF flow map, contrast may be adjusted. When considering areas to be analyzed for flow, the HRF also provides contrast and brightness adjustments that can be useful in identifying capillary beds. In Figure 2.177, both the brightness and contrast have been increased to better visualize the capillaries present in the image. In Figure 2.178, all Doppler maps have been enhanced to increase visualization of the capillaries. This manipulation of the image appearance does not affect any measurement.

Description of HRF blood flow measurements is not a trivial topic. Previously in this section, blood flow has been described as being measured in milliliters per minute per gram. This standard is sufficient when

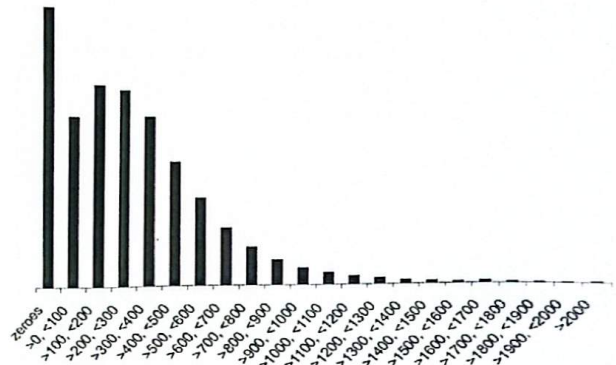


FIGURE 2.179

considering quantities of tissue that contain more than one capillary. HRF measurements contain volumes of tissue smaller than anything previously considered. The individual flow measurements may be completely filled with a capillary or may contain tissue in between capillaries, which is devoid of vessels. The measurement of flow in tissue between capillaries is zero. If this is the case, then the classic definition of flow loses meaning. If all individual flow measurements from the peripapillary retina are displayed on a histogram (Figure 2.179), two properties of retinal blood flow distribution become apparent:

1. Flow values within the tissue are not normally distributed.
2. A large number of pixels have a flow measurement of "0."

These zero-flow pixels may represent areas of tissue located between capillaries. In Figure 2.180, at higher magnification the measurement of zero-flow black pixels in the space between capillaries can be seen. The percentage of total pixels with values of zero is recorded

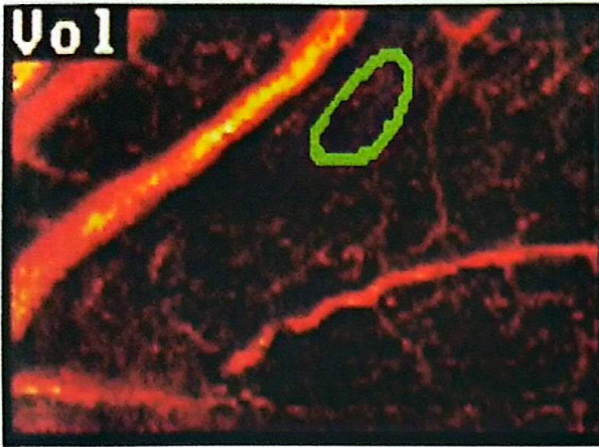


FIGURE 2.180

and used to represent vascular density. Should capillaries be recruited in response to increased metabolic demand, the percentage of zeros would decrease.

Removing the zeros from the histogram, the remaining data is skewed to the right (Figure 2.181). Descriptive statistics assume a normal distribution, and therefore the use of average and standard deviation values to describe the HRF data set is inaccurate. A cumulative percentage curve identifies the rate at which flow measurements accumulate within the histogram. Using this curve as a "look-up" tool, various landmarks on the distribution can be identified (Figure 2.182). The GRDC uses the 10th, 25th, 50th, 75th, and 90th percentile values to describe the distribution of HRF flow data (Figure 2.183). Using this technique of individual point-by-point analysis (pointwise analysis), HRF images from eyes with retinal ganglion cell loss have been

studied. These eyes present with increased zeros but also feature higher extreme flow values. These may represent a higher choroidal contribution to the signal detected by HRF (Figure 2.184).

An automated software package currently available for the HRF (Scanning Laser Doppler Flowmetry) averages all measurements with its surrounding flow measurements before analyzing the data set (Figure 2.185). It provides automated measurements of the average distance between capillaries (Figure 2.186). Unfortunately, after smoothing the data, capillaries are no longer evident in the image. To its credit, the software allows the user to identify the disc margin and disc orientation, after which it will provide data from various structures on and around the disc (Figure 2.187). Further, it provides a 95% confidence interval based on normative data and plots the current HRF flow distribution within that confidence interval (Figure 2.188). Note the distortion of the HRF data set that occurs when the data is first smoothed (Figure 2.189). The characteristics of flow in the retina are lost. Comparison of the distribution in Figure 2.190 and the distribution of raw HRF values in Figure 2.193 shows the two prominent features of the distribution of HRF flow measurements are eliminated. Despite the fact that data smoothing eliminates zeros (unless you happen to have a 5×5 block of data entirely composed of zeros, in which case the single pixel in the center would retain its original value), the SLDF flow package also is said to provide a measurement of the average distance between capillaries (Figure 2.191). This presents an impressive challenge because smoothing obscured the vessels before these distance measurements were performed. In this magnified view of an image before and after smoothing, the disappearance of distinct capillaries within the image as a result of smoothing is unmistakable (Figure 2.192). The effect of smoothing on the distribution is also

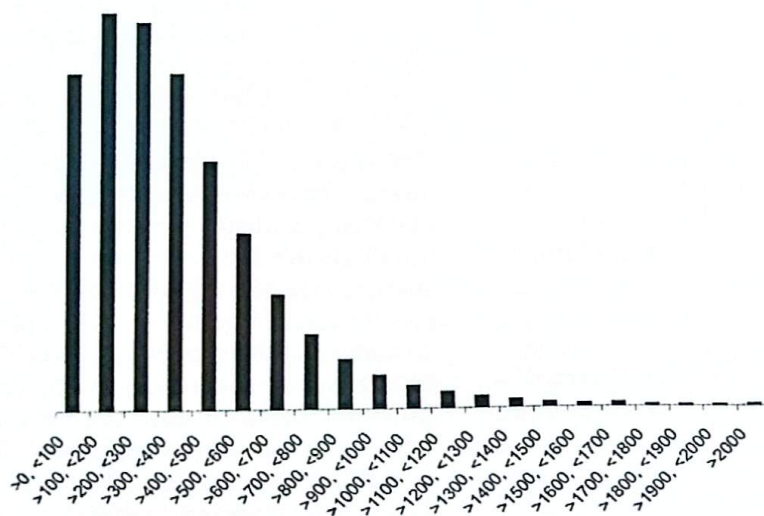


FIGURE 2.181

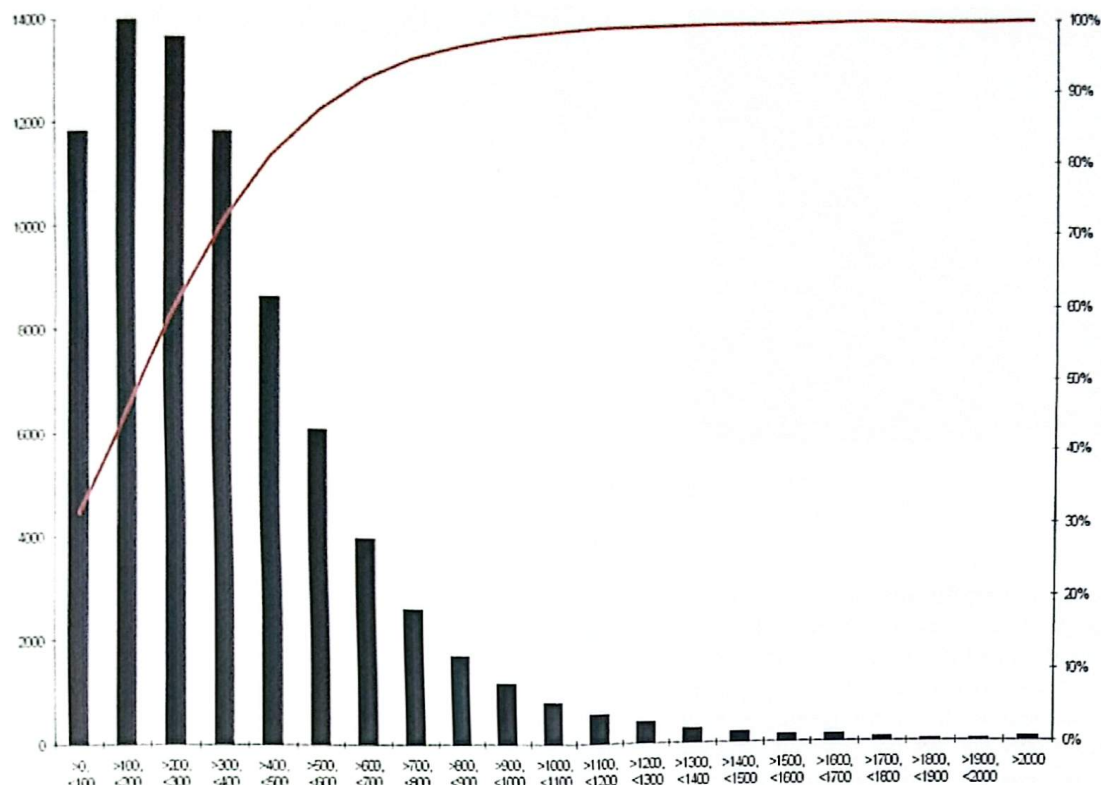


FIGURE 2.182

Avascular	17.00%
10%	0
25%	63.43
50%	240.18
75%	432.28
90%	658.11
95%	845.03
99%	1304.71
100%	2342.43

FIGURE 2.183

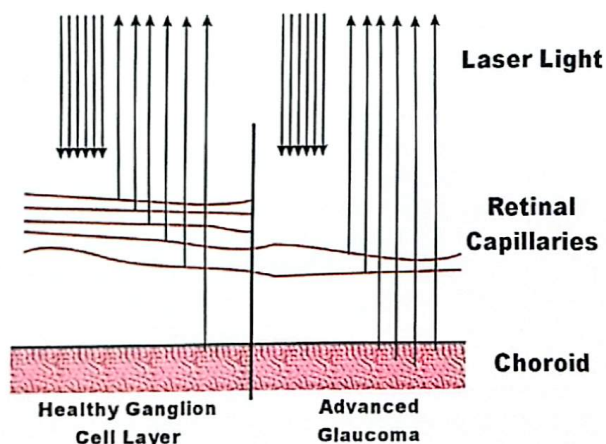


FIGURE 2.184

conspicuous. In Figure 2.193, individual flow values are once again presented before and after the sweeping 5×5 pixel average smoothing process has occurred. Data averaging (smoothing) unmistakably distorts HRF data. If it were not for this error in analysis, the SLDF software would provide an excellent solution to the problem of HRF data analysis.

To its advantage, the HRF measures volumetric flow, although in arbitrary units. Further, the HRF represents an important advance in hemodynamic analysis. With subcapillary resolution, the device has forced us to reconsider how we approach the description of blood flow. Although the exact meaning of HRF blood flow measurements remains unclear, studies with in vitro models have shown that the HRF is sensitive to small changes in blood flow (Figure 2.194).

The greatest disadvantage of the HRF is that flow measurements are in arbitrary units. The gold standard of milliliters per minute per gram has not been met, and it is unlikely that the current instrument will ever produce absolute measurements of blood flow. In studies with an in vitro model and a follow-up study in humans, the instrument was shown to be susceptible to errors caused by improper sensitivity settings (Figure 2.195). Both the LDF and HRF have identified reduced blood flow in subjects with glaucoma compared with healthy control subjects. HRF has also quantified reduced vascular density in glaucomatous eyes (Figure 2.196).

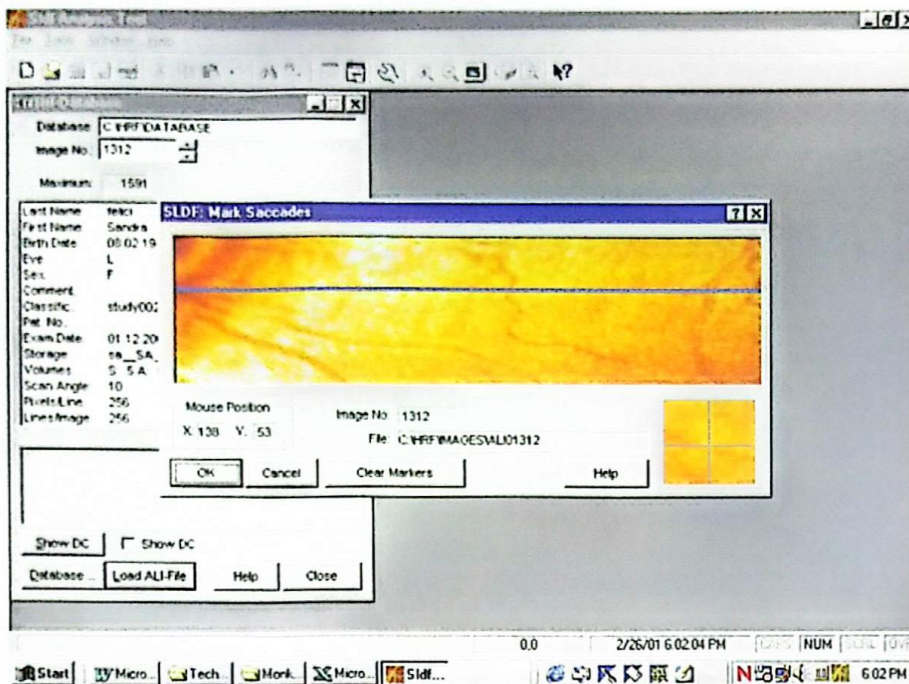


FIGURE 2.185

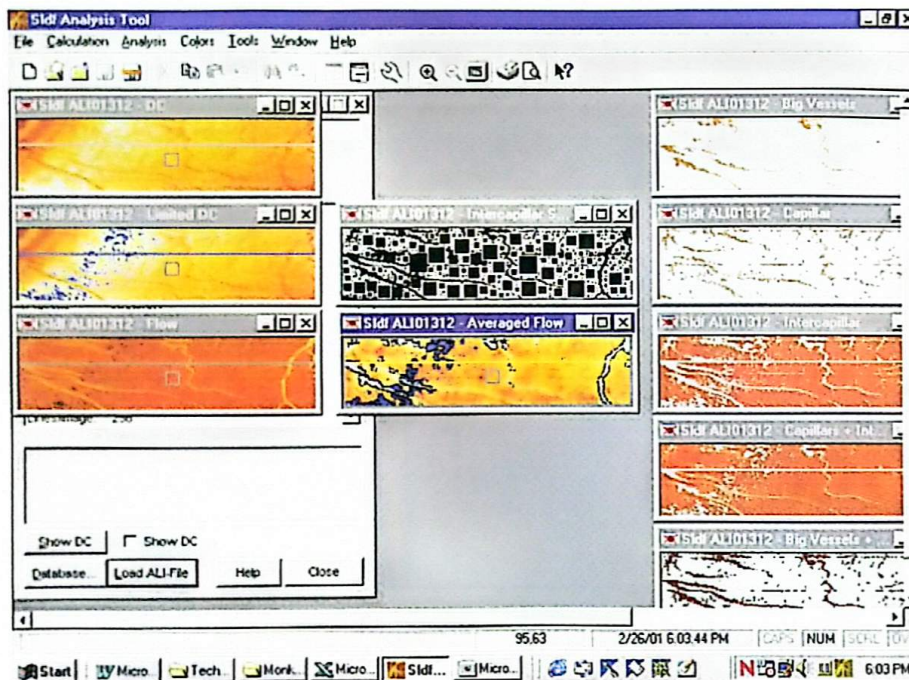


FIGURE 2.186

Color Doppler Imaging

The imaging methods discussed up to this point have focused primarily on devices that make measurements based on the reflection and scatter of light. Valuable diagnostic information also may be obtained by projecting sound into the body and observing how it is reflected and scattered. Color Doppler imaging (CDI)

(CDI, Siemen's Quantum 2000, Siemens Ultrasound Group, Issaquah, WA.), or ultrasound, is a common imaging technology used extensively in radiology, cardiology, and obstetrics (Figure 2.197). Sound waves move much slower than light. The CDI probe emits sound waves and uses the time taken for echoes to return to map structure and movement (Figure 2.198). Ultrasound imaging devices can use this information to

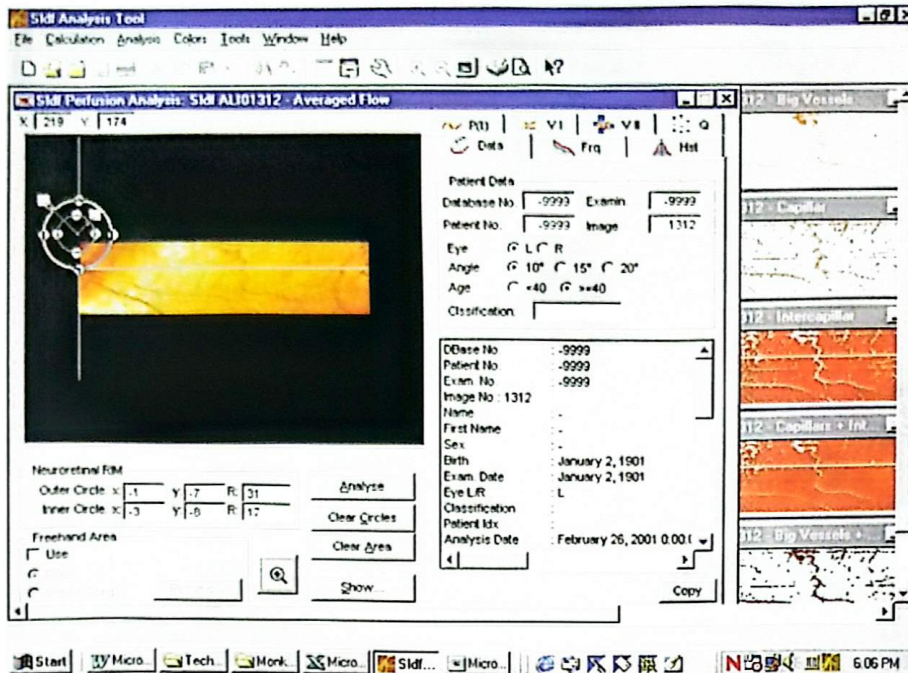


FIGURE 2.187

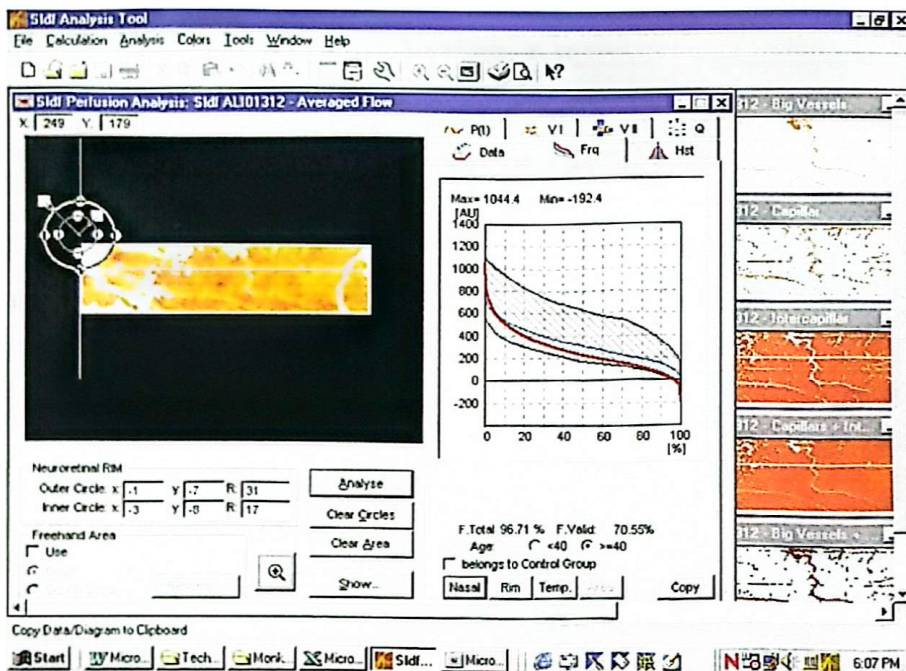


FIGURE 2.188

quantify the exact location of the sources of reflection within the body. The same Doppler effect described for the light wave-based technologies also applies to sound waves reflected from moving sources. The frequency of sound waves striking moving reflective sources is Doppler shifted (Figure 2.199). CDI measures Doppler shifts to quantify velocities.

Consider the stationary reflective sources within the eye. Ultrasound performed on a line from a single point (an "A-scan") can identify the depths of various reflective layers (Figure 2.200). If a number of A-scan probes are arranged in a line, the resulting depth measurements could be assembled to form an image (Figure 2.201). This is how a linear array probe is

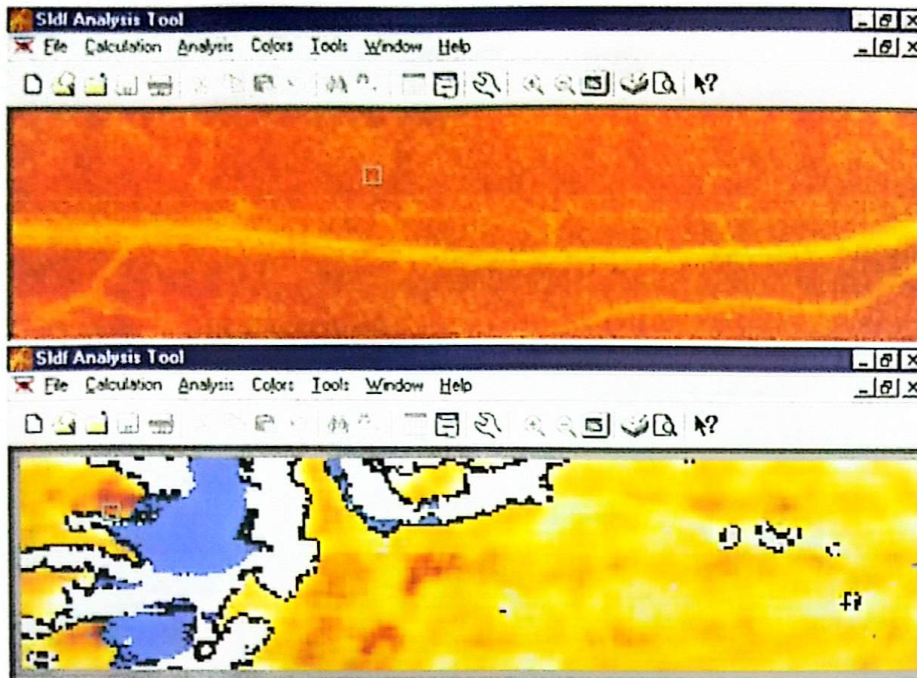


FIGURE 2.189

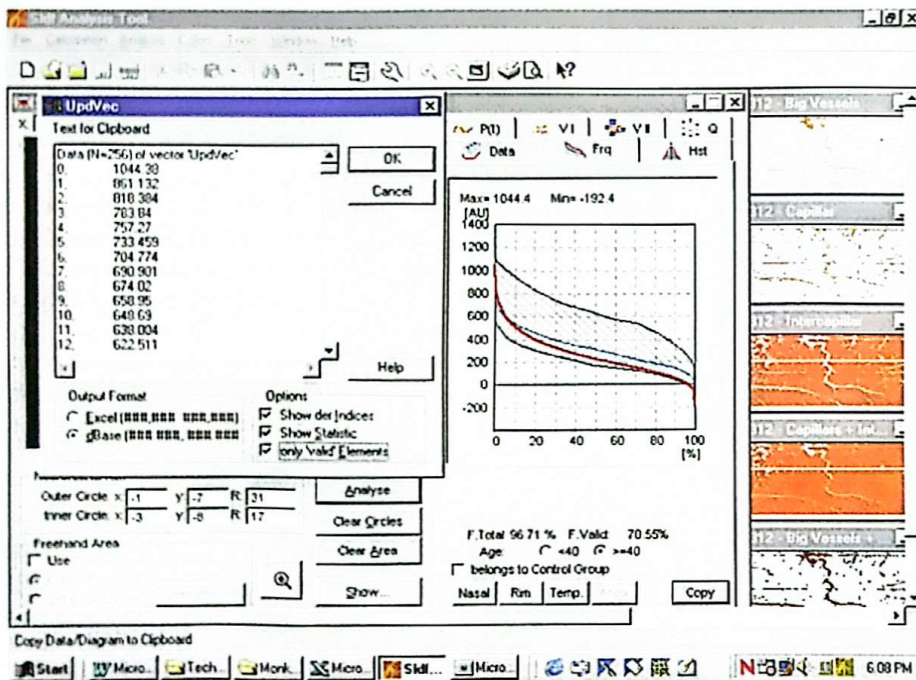


FIGURE 2.190

configured. By locating the distance of structures from a number of measurement points arranged in a line, the B-scan creates an image slice through the globe. Figure 2.202 is a B-scan of a healthy eye. The cornea is visible on the far left, and the posterior surface of the lens is highly reflective. The black bullet-shaped structure within the fatty tissue on the far right of the image is a slice through the optic nerve.

CDI examinations begin by applying sterile ultrasound coupling gel to the linear array ultrasound probe (Figure 2.203). The probe is then placed on the closed eyelid (Figure 2.204). Care is taken to minimize pressure on the globe. As long as there is a continuous layer of gel between the probe and the eyelid, no pressure is necessary to obtain a good image. If the patient has difficulty with eye movements, the fellow

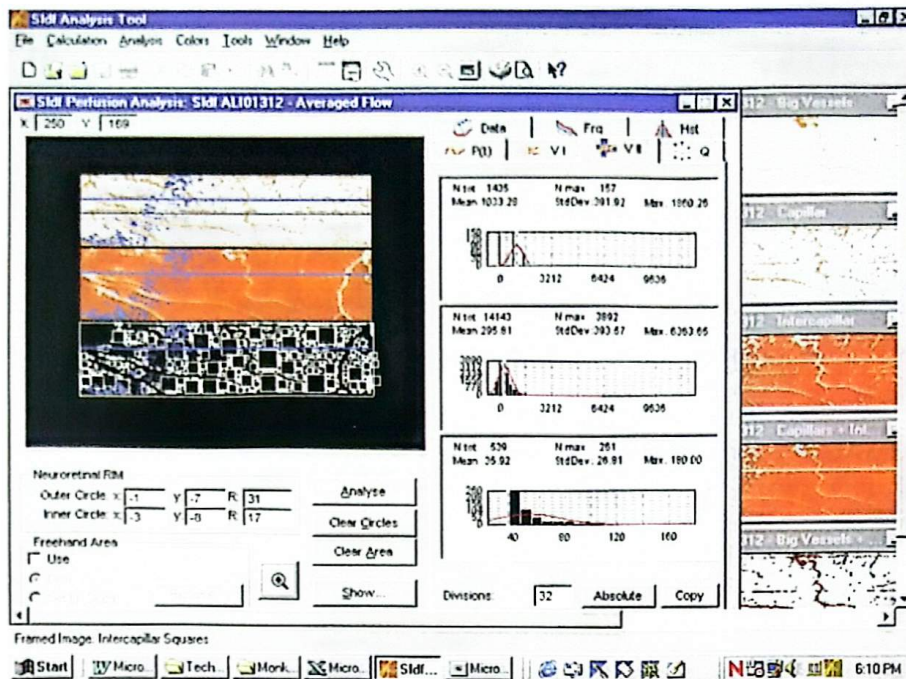


FIGURE 2.191

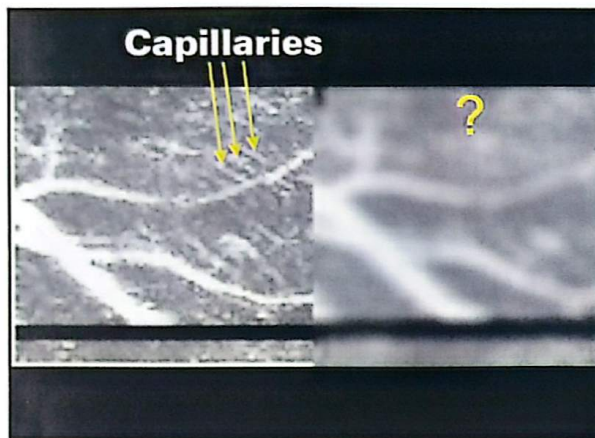


FIGURE 2.192

eye can be open and used to fixate on a target. The ultrasound technician focuses on the video image while scanning the orbit (Figure 2.205). Because the technician focuses attention on the video monitor, he or she must use her sense of feel to monitor the location of the probe relative to the patient's eye. Therefore, the technician holds a finger against the patient's cheek to monitor the distance between the probe and the eye (Figure 2.206). The cord of the ultrasound probe is supported by the technician's shoulders and arm to avoid fatigue during the exam (Figure 2.207). To take the weight of the probe off the arm, the technician rests the base of the hand on the patient's forehead, both to avoid fatigue and to reduce pressure on the globe. With proper technique, a high

level of probe control is maintained (Figure 2.208), which is essential for accurate assessment of vessels with diameters between 80 and 200 μm .

The technician's other hand operates the CDI control panel, pictured in Figure 2.209. During imaging, the sensitivity and depth settings are frequently adjusted, especially when moving from one vessel to another. In Figure 2.210, the depth setting, "42 mm," and velocity range, "low," are displayed on the ultrasound screen and circled in yellow. *Low* implies velocities within a low range of values and is appropriate for assessment of the central retinal artery (CRA) and posterior ciliary artery (PCA) interrogation. Ophthalmic artery (OA) velocities would saturate (be above the range of sensitivities of) the CDI on the low setting.

Figure 2.211 presents two images of the same eye obtained using a deep scan with low sensitivity to movement and a shallow scan with high sensitivity to movement. Note the difference in presentation of the low-velocity vessels (PCAs and CRA) in and around the optic disc. To actually measure the velocity within one of these vessels, the vessel of interest is located, and the green bars or sample gate are placed over the vessel (Figure 2.212). The CDI will measure velocity from the tissue located between the bars. Velocity is graphed on the y-axis, against time on the x-axis (Figure 2.213). The velocity waveform differs between vessels and may be used to confirm the vessel being inspected. The technician identifies the peak systolic and end-diastolic velocities from the velocity waveform (Figure 2.214). Pourcelot's resistive index is automatically calculated from the velocity measurements and is associated with

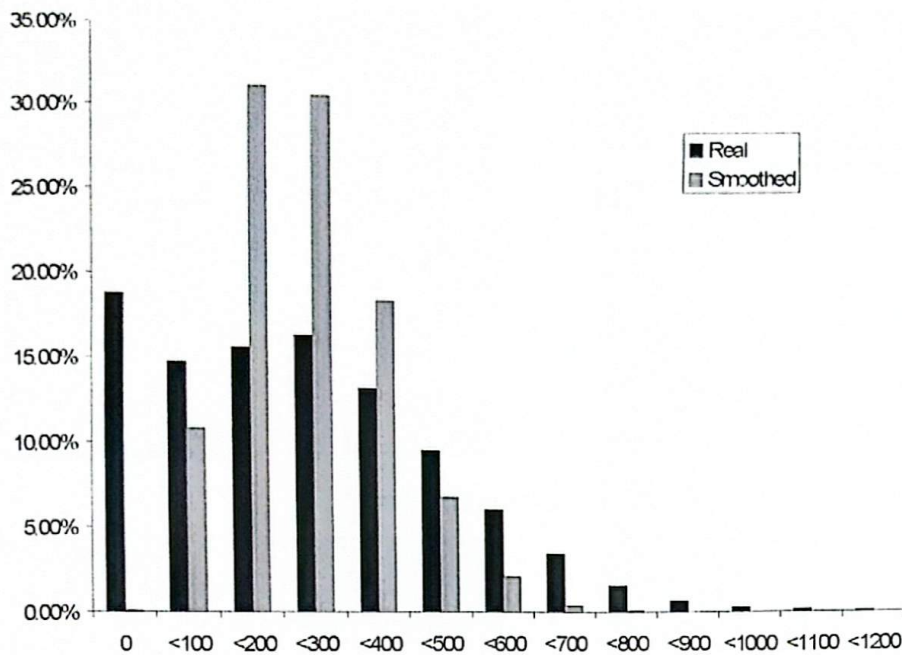


FIGURE 2.193

Pros
- Volumetric flow measurement - Validated by multiple in vitro models

FIGURE 2.194

Health and Disease
- Both LDF and HRF find lower temporal than nasal flow in normals - Glaucoma patients present with lower vascular density than age matched normals

FIGURE 2.196

Cons
- Measurements are in arbitrary units, and will never be absolute - Flow measurements are affected by noise - Rim data requires a difficult image acquisition technique

FIGURE 2.195

resistance in the vascular beds being perfused by the artery being measured (Figure 2.215).

In summary, CDI has several advantages, compared to the previously described optical imaging techniques

(Figure 2.216). To its favor, CDI is a noninvasive procedure that allows hemodynamic data to be obtained from eyes which have poor optical media. A clear view of the fundus is not required; therefore patients with cataracts or non-dilated pupils can be readily examined.

On the other hand, use of CDI technology does not come without its own set of problems. The device itself is very expensive, and reproducible data requires an experienced technician (Figure 2.217). Excessive pressure on the eye when using the ultrasound probe may acutely alter IOP, changing the velocities being measured. In addition, CDI contrasts from previous techniques as it is the only ocular hemodynamic measurement that is not performed with the patient in a sitting position. In younger patients it is often difficult to locate the PCAs because the strong activity of the OA masks their appearance to the probe. The CRA has the worst reproducibility, with coefficients of variation over



FIGURE 2.197

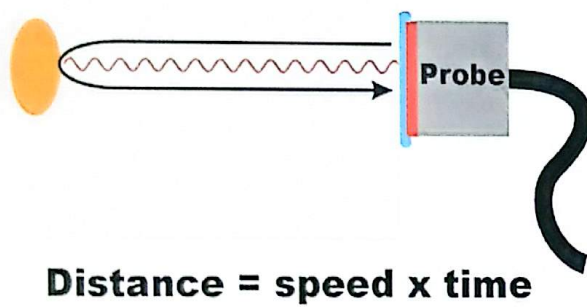


FIGURE 2.198

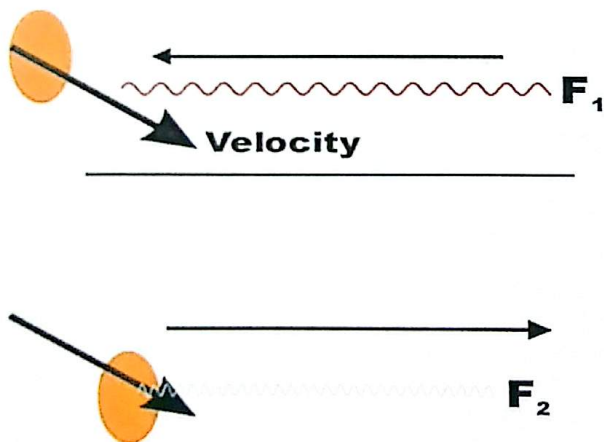


FIGURE 2.199

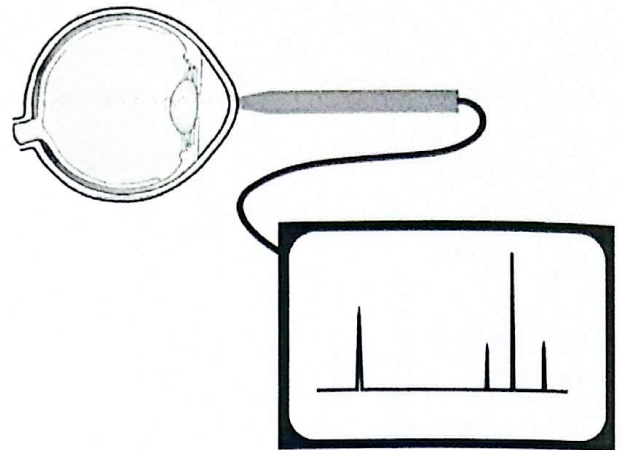


FIGURE 2.200

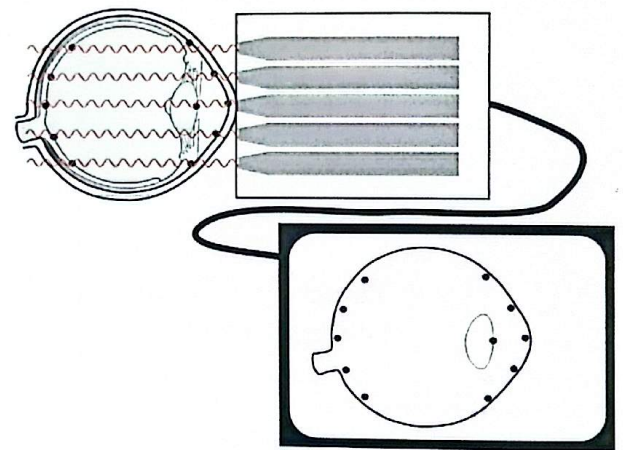


FIGURE 2.201



FIGURE 2.202



FIGURE 2.203



FIGURE 2.206



FIGURE 2.204



FIGURE 2.207



FIGURE 2.205

17% (Figure 2.218). The PCAs have the most reproducible velocity measurements, with coefficients of variation less than 10%.

Patients with glaucoma, AMD, and diabetic retinopathy have all displayed velocity measurements



FIGURE 2.208

lower than age-matched controls (Figure 2.219). Patients with NTG have presented with reversible vasospasm within their ocular vasculature. Figure 2.220 is an image obtained from a patient with nearly 100% blockage of the right internal carotid artery. The direction of flow in the



FIGURE 2.209

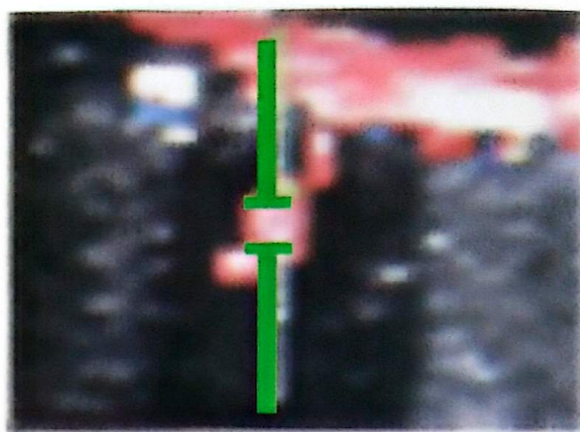


FIGURE 2.212



FIGURE 2.210

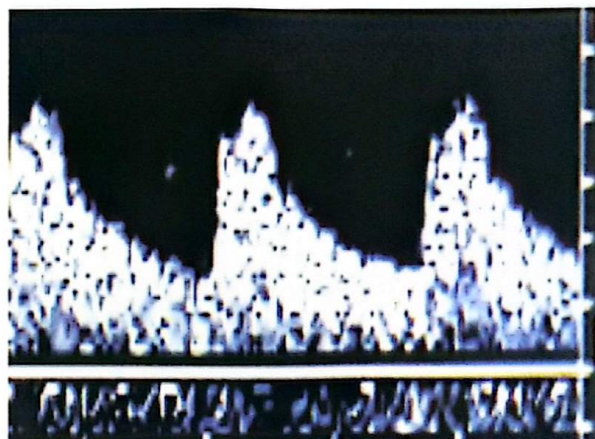


FIGURE 2.213

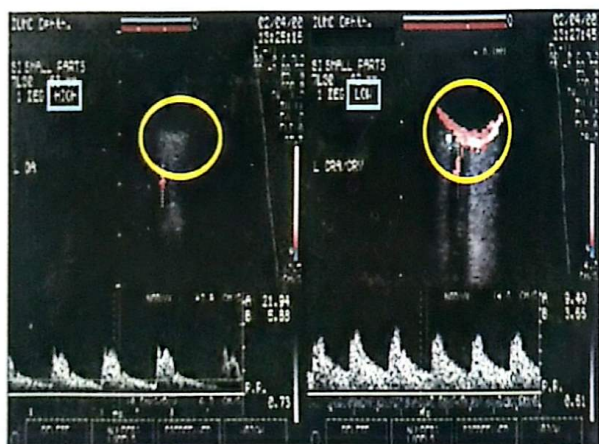


FIGURE 2.211

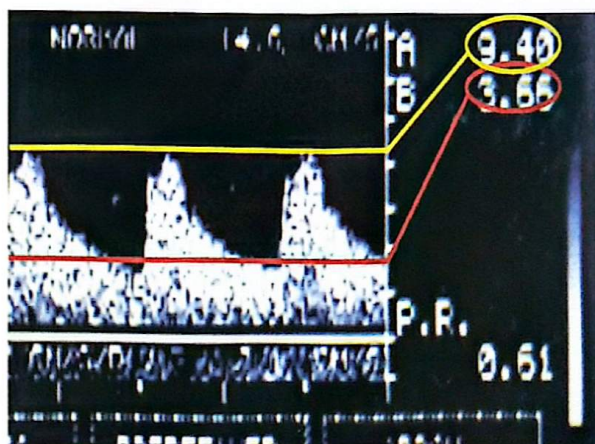


FIGURE 2.214

Resistive Index

$$\text{Pourcelot's Resistive Index} = \frac{\text{PSV} - \text{EDV}}{\text{PSV}}$$

FIGURE 2.215

Reproducibility

	PSV	EDV	RI
OA	5.1%	9.6%	1.7%
CRA	5.3%	17.9%	4.6%
TSPCA	11.6%	8.8%	7.6%
NSPCA	12.0%	14.2%	4.9%

FIGURE 2.218

Pros

- Data not effected by poor ocular media
- Noninvasive
- Absolute velocity measurements can be confirmed with phantoms

FIGURE 2.216

Health and Disease

AMD vs Controls: OA ↔
 N&T PCA - EDV & PSV ↓ RI ↔
NTG: OA EDV ↓ RI ↔
POAG: CRA & PCA PS/EDV ↓
Asymmetric Fields:
 CRA field ↓ RI ↑

FIGURE 2.219

Cons

- \$250,000
- Reproducibility requires experience and skill
- Ocular pressure can increase IOP

FIGURE 2.217



FIGURE 2.220



FIGURE 2.221

right OA was reversed with reduced flow in the CRA and PCAs. In the same patient, the flow direction in the left OA, the side with the unblocked internal carotid artery, was in the normal direction and higher than in healthy participants (Figure 2.221).

Other Vessel Measurement Devices

RETINAL VESSEL ANALYZER (RVA)

The Retinal Vessel Analyzer (RVA) from Zeiss Jena produces real-time diameter measurements of large retinal vessels with a spatial resolution of less than $1\ \mu\text{m}$. This is accomplished through a statistical process. The physical resolution of the device is approximately $17\ \mu\text{m}$ per pixel. By performing a rapid series of vessel diameter measurements and maintaining a floating average over time, the device has demonstrated the ability to accurately monitor the pulsation of retinal vessels throughout the cardiac cycle.

The patient's eye must be dilated for an RVA exam. The device consists of a modified retina camera (FF450 from Zeiss GmbH; Jena, Germany). A charged-coupled-device (CCD) camera is fitted to the retina camera and creates an analog video image of the fundus. In a procedure similar to that used in fundus photography, the fundus camera is positioned to maximize fundus image quality, with vessels of interest near the image center. The examiner views the live video image on the monitor, and selects the desired measuring area. The area is selected by manually drawing proximal and distal boundaries across the vessel of interest on either the y- or x-axis. Picture sequences are digitized in real time using a PC equipped with a digitizer.

Measurements across the vessel are rapidly made in random order at each pixel location between the two boundary markers. Each diameter measurement, its location on the vessel, and the time of measurement are recorded. For each frame of video, the vessel brightness profile within the user-designated segments are digitized and analyzed with a measuring program. Estimated diameters are recorded digitally.

The instantaneous vessel diameter was defined as the local (temporal and spatial) statistical expected mean. The standard deviation of vessel diameter is used as a measure of temporal variation.

RVA measurement variables include:

Local measuring resolution in measuring direction:	1 μm (interpolation)
Vessel segment length	70 to 300 μm
Local measuring resolution in vessel direction	186 μm
Maximum local scan area	0.186 to 5 mm
Measuring time for single value	40 ms
Measuring time range	40 ms to 10 minutes
Measuring frequency	>1/25 second
Measuring image field (angle)	40°

The RVA provides information on vascular tone and may be useful in examining the effect of vasoactive compounds on the large retinal vasculature. However, the instrument may be insensitive to changes in the peripheral vascular tone or changes in blood flow caused by altered blood rheology. The second factor may be important in disease; for example, blood chemistry is altered in glaucoma patients. Therefore, the instrument is most suitable for clinical research in the areas of vascular autoregulation and is most revealing when used in combination with a retinal hemodynamic assessment device.

Conclusion

No single technique measures all vascular beds. The CLBF alone can measure volumetric blood flow, but it is limited to large retinal vessels in patients with clear optical media. By combining the various technologies that are currently available, it is possible to accumulate substantial information describing hemodynamics in the retinal macrocirculation, retinal microcirculation, choroid, and retrobulbar arteries. The clinical meaning of cohort data or a single snapshot in time remains unclear. The current level of technology, however, is sufficient to document and monitor diminutive changes in each of these vascular beds.

Principal Clinical Applications with Examples of Altered Circulation

Common Maculopathies

AGE-RELATED MACULAR DEGENERATION

Traditionally, investigators have believed that senescence of the retinal pigment epithelium (RPE), which metabolically supports and maintains the photoreceptors, leads to age-related macular degeneration (AMD). Senescent RPE accumulates metabolic debris as remnants of incomplete degradation from phagocytosed rod and cone membranes. Progressive engorgement of these RPE cells leads to drusen formation with subsequent further dysfunction of the remaining RPE. Consequently, sunlight may contribute to RPE senescence through photochemical damage via the production of activated forms of oxygen. In the Maryland Waterman survey, advanced macular degeneration was more common in men exposed to increased levels of blue light, but not with increased ultraviolet exposure (West, Rosenthal, Bressler, et al., 1989; Bressler, Munoz, Maguire, et al., 1995). Likewise, the Beaver Dam Eye Study found that exposure to visible light was associated with macular degeneration. Similarly, nutrition may play a role in minimizing macular degeneration via RPE senescence (Cruickshanks, Klein, Klein, 1993). Some investigators speculate that antioxidants such as vitamin C and vitamin E, as well as the carotenoids found in the macula (lutein and zeaxanthin), may protect against macular degeneration by limiting oxidative damage (Mares Perlman, Brady, Klein, VandenLangenberg, Klein, 1995; Seddon, Ajani, Sperduto, et al., 1994; Mares Perlman, Brady, Klein, et al., 1995). In some studies, for example, higher blood levels of beta-carotenes and carotenoids were associated with a decreased risk of macular degeneration. The Age-Related Eye Disease Study (AREDS) a multicenter, prospective, NIH-supported trial, has shown that antioxidants plus zinc decreased the risk of developing advanced AMD in subjects with intermediate AMD (*Arch Ophthalmol* 2001 Oct;119(10):1417-1436).

Although the theory of RPE senescence is appealing, it does not fully account for the wide variety of clinical presentations in AMD, including various forms of drusen, hyperpigmentation, and RPE atrophy in nonexudative AMD, as well as choroidal neovascular membrane (CNVM) formation in exudative AMD. For example, it is

unclear why a primary RPE defect would cause an atrophic macular lesion with loss of the underlying choroidal blood supply, the choriocapillaris.

Consequently, a second pathogenic theory involves primary vascular changes in the choroid, which then secondarily affect the RPE and lead to AMD (Friedman, 1997). Further, both theories may apply because non-exudative AMD, with its widely varying clinical presentations, may actually represent several distinct disorders that have yet to be more clearly differentiated on a pathogenic basis; it is possible that RPE senescence represents the primary derangement in some subforms and that choroidal perfusion defects represent the primary derangement in other subforms. For example, the choriocapillaris is known to supply the metabolic needs of the RPE and the outer retina; a primary perfusion defect in the choriocapillaris could account for the physiologic and pathologic changes in AMD, including RPE and Bruch's membrane abnormalities. Some authors, for instance, have suggested that prolonged choroidal filling may correlate with diffuse thickening of Bruch's membrane.

Prolonged choroidal perfusion has been noted angiographically in patients with exudative AMD, and some evidence has shown choroidal blood flow to be abnormal in patients with nonexudative AMD (Boker, Fang, Steinmetz, 1993; Remulla, Gaudio, Miller, Sandberg, 1995; Zhao, Frambach, Lee, Lee, Lopez, 1995). Eyes with prolonged choroidal filling angiographically have been shown to harbor discrete areas of increased threshold on static perimetry (Chen, Fitzke, Pauleikhoff, Bird, 1992). In addition, prolonged choroidal filling appears to be independently associated with loss of vision; in one study, 38% of 32 eyes with this sign lost two or more lines of vision by 2 years compared with 14% of 64 eyes without this sign (Piguet, Palmvang, Chisholm, Minassian, Bird, 1992). This difference was related to the greater incidence of geographic atrophy in the patients with prolonged choroidal filling; significantly, the incidence of CNVM was similar in each group of patients.

Choroidal blood flow is difficult to quantify angiographically, given the overlying retinal circulation and multilayered choroidal circulation that complicates analysis. One group recently used a new analysis technique based on indocyanine green (ICG) angiography

to compare the choroidal circulation in patients with AMD to a control group. They noted a statistically significant increased frequency of presumed macular watershed filling, which they described as "characteristic vertical, angled, or stellate-shaped zones of early-phase indocyanine green videoangiographic hypofluorescence, assumed to be hypoperfusion, which disappeared in the early phase of the angiogram" (Ross, Barofsky, Cohen, Baber, Palao, Gitter, 1998). Another group studied nonexudative AMD subjects using an area dilution analysis technique applied to ICG angiography (Ciulla, Harris, Kagermann, et al., 2002). In this study, mean intensity levels at specific locations in the macular area were graphed over time to yield dye dilution curves, which were then analyzed for dye appearance time, maximal fluorescence, and the rate of fluorescence buildup. This technique showed heterogeneity of filling and decreased flow within the choriocapillaris of patients with nonexudative AMD when compared with healthy participants. Two groups have previously used color Doppler imaging to evaluate the retrobulbar vasculature in AMD, and they found statistically significant lower flow velocities and resistive indices of the central retinal and posterior ciliary arteries in those with AMD compared with control subjects (Friedman, Krupsky, Lane, et al., 1995; Ciulla, Harris, Chung, et al., 1999). In a cohort study consisting only of patients with nonexudative AMD, one group used a new technique called laser Doppler flowmetry to show that the choroidal blood flow was decreased at the center of the fovea compared with a control group (Grunwald, Hariprasad, Du Pont, et al., 1998).

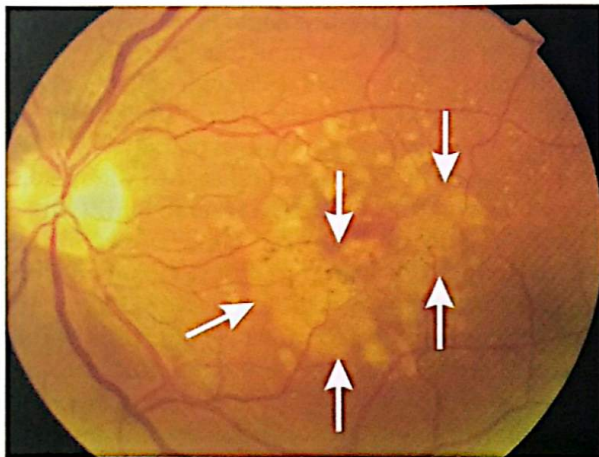


FIGURE 3.1 Left eye, color fundus photo of nonexudative AMD. Note the confluent soft drusen in the perifoveal region, as well as the coarse RPE clumping (arrows). Also, some hard drusen are located more peripheral to the fovea. These features are typical of nonexudative AMD, and this would be considered high risk given the soft confluent drusen and coarse RPE clumping.

Consequently, choroidal perfusion abnormalities undoubtedly exist in AMD. However, at this time, it is not possible to determine if these choroidal perfusion abnormalities play a causative role in nonexudative AMD; if they are simply associated with another primary alteration, such as a primary RPE defect or a genetic defect at the photoreceptor level; or if they are more strongly associated with one particular form of this heterogeneous disease (Ciulla, Harris, Martin, 2001). Clearly, future progress in developing effective treatment strategies for this devastating disorder hinges on a better understanding of disease development (Ciulla, 2001).

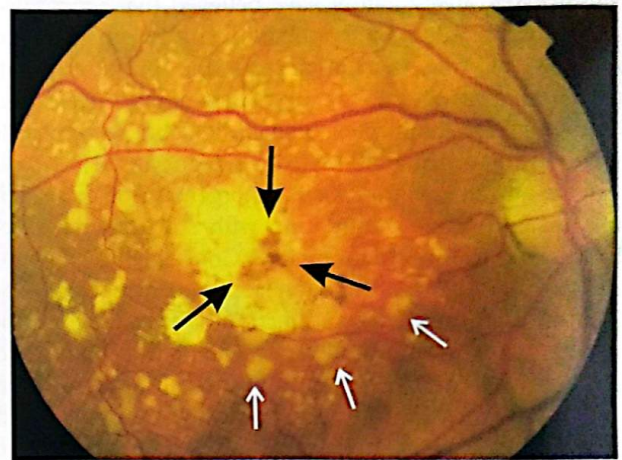


FIGURE 3.2 Right eye, color fundus photo of nonexudative AMD. Note the soft drusen (white arrows) and central RPE clumping (black arrows) typical of nonexudative AMD.

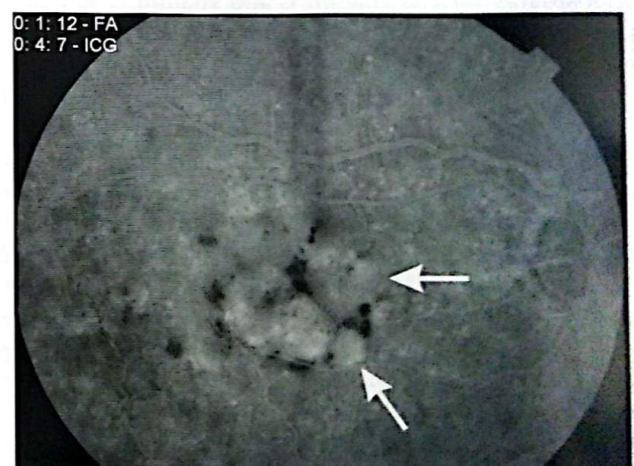


FIGURE 3.3 Fluorescein angiogram, 1'12" frame. The midframe of the angiogram reveals staining of the drusen (arrows) and blockage of the underlying choroidal fluorescence by the RPE mottling centrally. There is no leakage to suggest a CNVM.

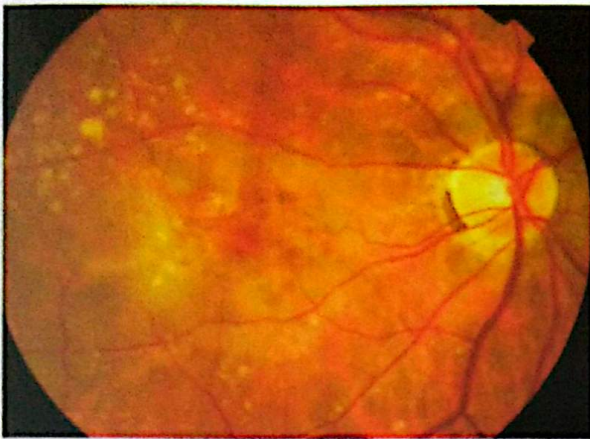


FIGURE 3.4 Right eye, color photo. Note the diffuse drusen and RPE changes consistent with AMD. In addition, central subretinal fluid and some early subretinal fibrosis are present, suggestive of CNVM caused by AMD.

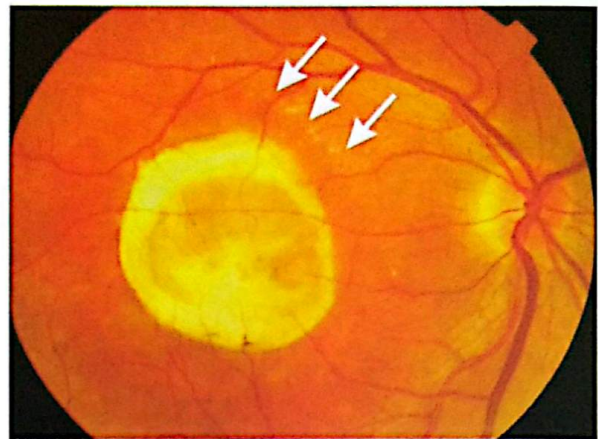


FIGURE 3.7 Right eye, color fundus photo of disciform scarring from the AMD. Note the central 4.5 disc area circular collection of subretinal fibrosis that is typical for disciform scarring from AMD. Note the hard drusen (arrows) superior-nasal to the lesion.

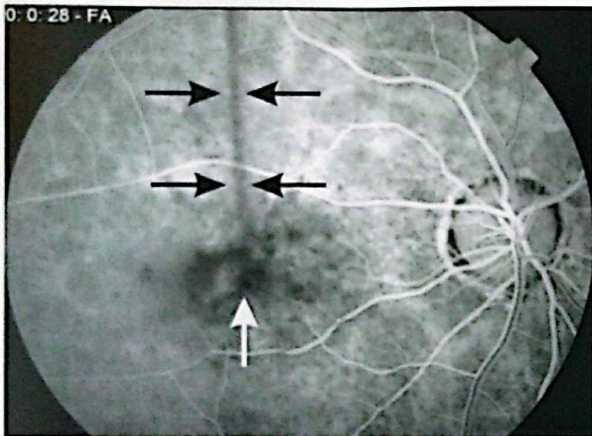


FIGURE 3.5 Same patient, 28" frame. This frame is taken from the laminar venous flow phase. Some mild and poorly defined hyperfluorescence is noted centrally. The fixation pointer (arrows) is used to confirm the central location of this lesion.

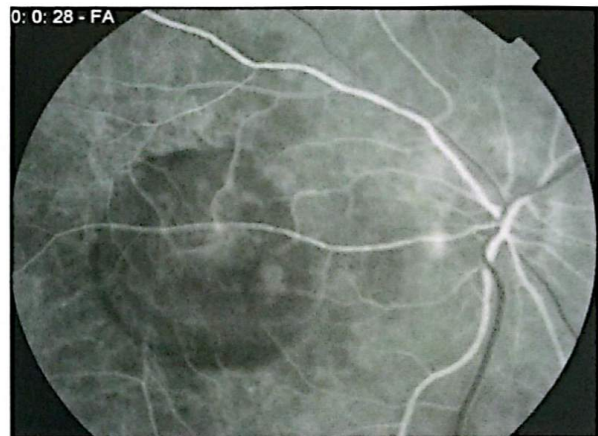


FIGURE 3.8 Frame, 28". This laminar venous flow phase angiogram reveals central hypofluorescence in the region of the disciform scar caused by subretinal fibrosis. At this stage the CNVM becomes less vascularly active, and this along with the blockage by the subretinal fibrosis leads to early hypofluorescence.



FIGURE 3.6 Same patient, 6'59" frame. This frame is taken in the late phase of the angiogram. Note the poorly defined, stippled central leakage. These early and late frames are consistent with an occult CNVM located subfoveally.

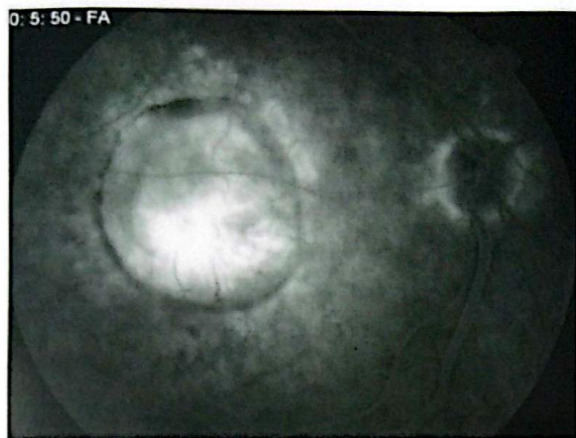


FIGURE 3.9 Same patient, 5'52" frame. The late frame of the angiogram reveals central staining of the disciform scar. Note that there is no leakage beyond the border of the lesion. The early hypofluorescence and late staining are typical of the disciform scars.



FIGURE 3.10 Right eye, color photo depicting a laser scar centered on the fovea and performed for a subfoveal CNVM. Note the absolute atrophy centrally.

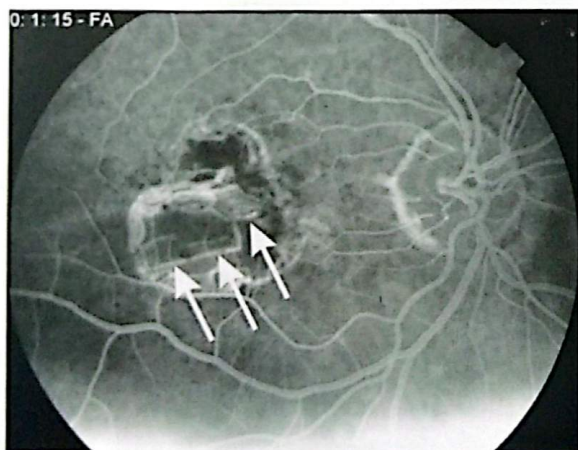


FIGURE 3.11 Right eye, posttransit fluorescein angiogram, 1'15" frame. Note the window defect centrally as a result of the laser scar. There is obliteration of the pigment epithelium and choriocapillaris, consequently allowing visualization of the large and deeper choroidal vessels (arrows).

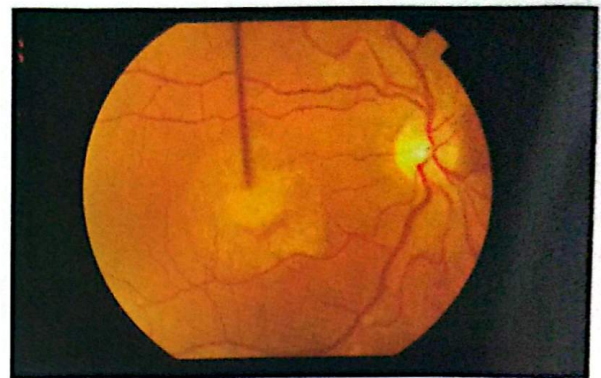


FIGURE 3.12 Right eye, color fundus photo of exudative AMD. Note the subretinal hemorrhage. (Courtesy Dr. C. W. Yung, Indiana University.)

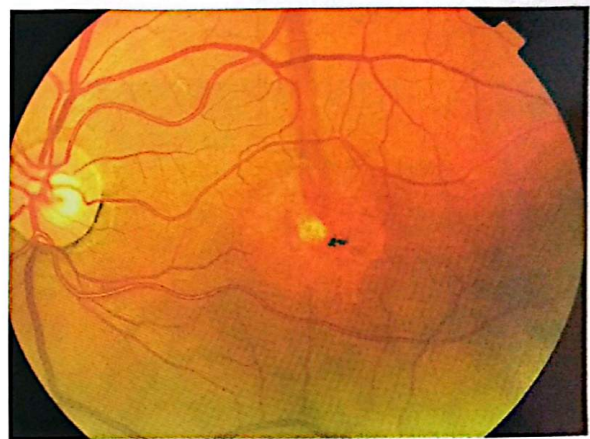


FIGURE 3.13 Left eye, color fundus photo of AMD with central atrophy and surrounding RPE mottling. (Courtesy Dr. C. W. Yung, Indiana University.)

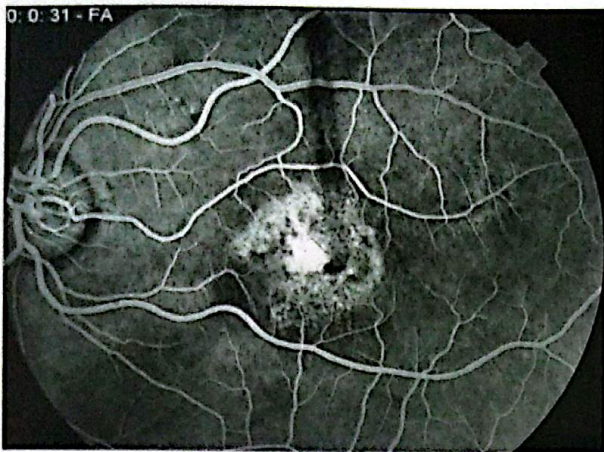


FIGURE 3.14 Same eye, fluorescence angiographic finding. Note the staining of the central atrophy and surrounding RPE mottling. (Courtesy Dr. C. W. Yung, Indiana University.)

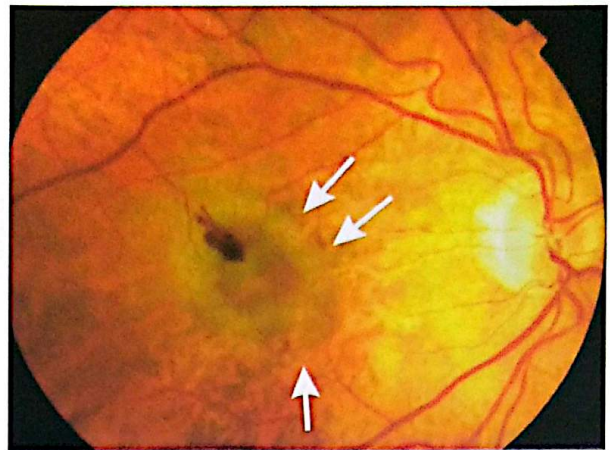


FIGURE 3.17 Right eye, color fundus photo. Note the 1.5 disc area subfoveal grey-green pigment, as well as the subretinal hemorrhage. In addition, there is faint subretinal hemorrhage at the nasal and inferior edge of the lesion (*arrows*). These features are all consistent with a subfoveal CNVM.

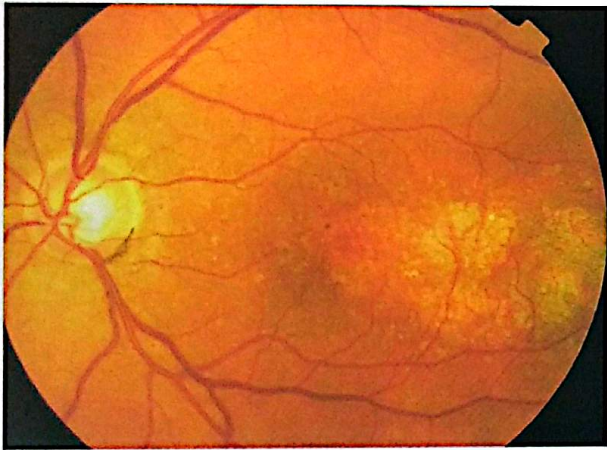


FIGURE 3.15 Left eye, color fundus photo showing atrophic changes involving the RPE. Note the underlying large choroids vessels are visible. (Courtesy Dr. C. W. Yung, Indiana University.)

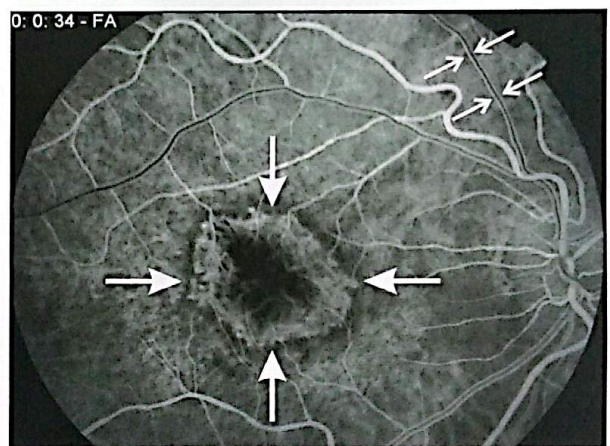


FIGURE 3.18 Same patient, fluorescein angiogram, 34" image. This frame is taken during laminar venous flow, as evidenced by the fluorescein at the peripheral edges of the veins, yielding a striped appearance (*small arrows*). The arteries have already filled. Note a 1.5 disc area region of discrete hyperfluorescence in the subfoveal region, correlating with the findings of the color photo. Subfoveal vessels are visible (*large arrows*), as well as a hypo-fluorescent ring around the lesion, all of which is consistent with the subfoveal classic, well-defined CNVM.

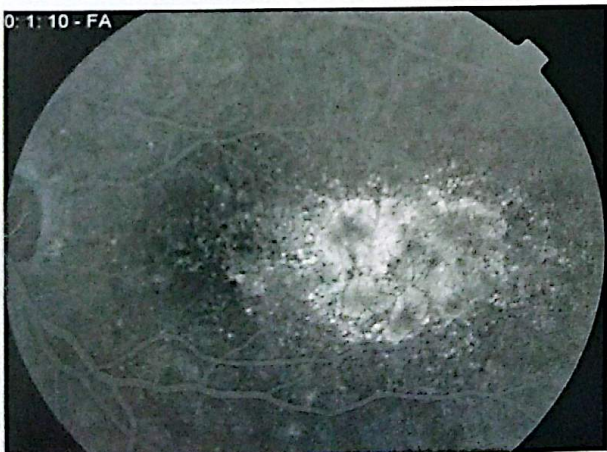


FIGURE 3.16 Fluorescein angiogram of the same eye, 1'10" frame, showing the staining of the atrophic changes. (Courtesy Dr. C. W. Yung, Indiana University.)



FIGURE 3.19 Same eye, 7:55" frame. The late frames of the angiogram show intense leakage from the subfoveal lesion, confirming the presence of the subfoveal CNVM. Hemorrhages block the underlying fluorescence, as noted clinically.



FIGURE 3.20 Right eye, color fundus photo showing exudative AMD with a subfoveal CNVM. Note the drusen in the superior macula, the subfoveal hemorrhage, and pigmented lesions suggesting a subfoveal CNVM.

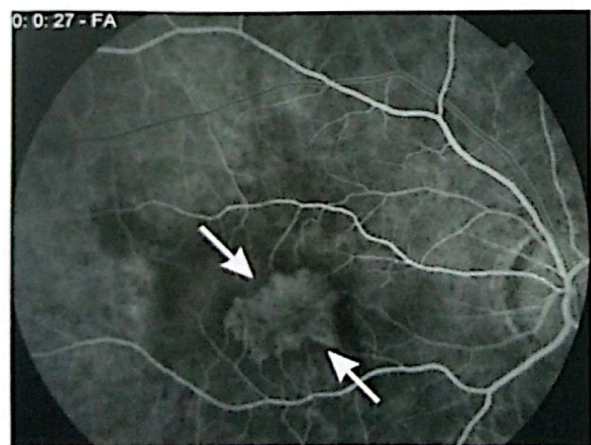


FIGURE 3.21 Same patient, 27" fluorescein angiography frame, early laminar venous flow phase. Note the well-defined 1 disc area region of discrete hyperfluorescence and a cartwheel pattern delineating the larger vessels within the CNVM (arrows).

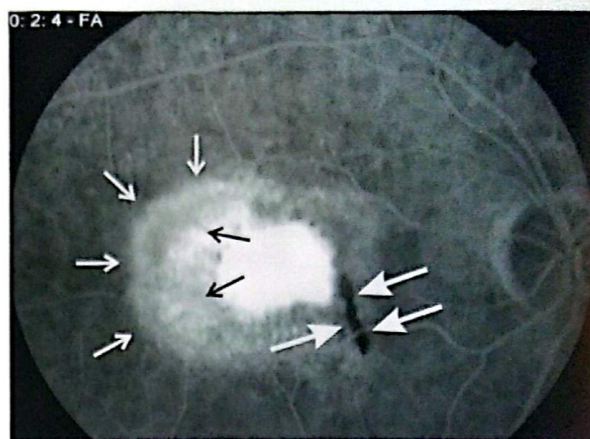


FIGURE 3.22 Same patient, 2:4" frame. The posttransit frame of the angiogram reveals leakage from the well-defined subfoveal complex, consistent with the classic subfoveal CNVM measuring approximately 1 disc area. There is surrounding poorly defined, stippled hyperfluorescence (*small arrows*) suggestive of an occult component. In addition, some blockage by the subretinal hemorrhage is seen clinically (*large arrows*).



FIGURE 3.23 Same patient, 6:21" frame. The late frame of the angiogram confirms the leakage at the classic component located subfoveally and also at the occult component surrounding this complex. Consequently, this is characteristic of a mixed classic plus occult CNVM.

MYOPIA/TILTED DISC



FIGURE 3.24 Left eye, color fundus photo of myopic degeneration. Note the peripapillary atrophy, oblique insertion of the disc, prominent choroidal markings visible through the attenuated RPE, and the lacquer cracks in the inferior perifoveal region (arrows).

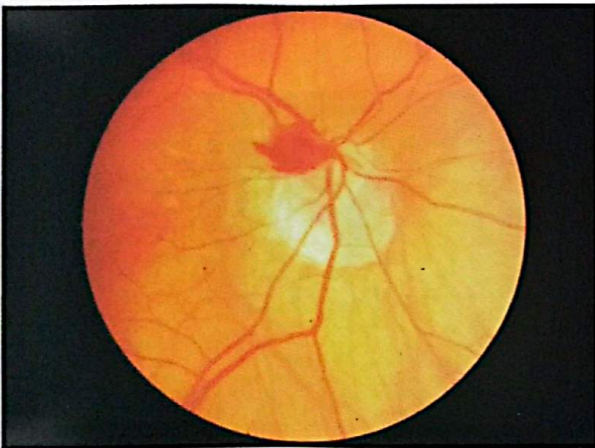


FIGURE 3.25 Marked peripapillary hemorrhage in tilted disc anomaly.

CENTRAL SEROUS RETINOPATHY

Central serous retinopathy, a common disorder predominantly affecting young men who develop neurosensory retinal detachments, has a somewhat controversial pathogenesis. The choroidal circulation, which provides 80% to 85% of ocular blood flow, is difficult to study by fluorescein angiography, which cannot delineate the choroidal circulation behind the relatively opaque RPE. In recent years, ICG with scanning laser ophthalmoscopy and image processing technology has been used to study the role of the choroid in this disorder (Prunte, 1995; Prunte, Flammer, 1996). In one study, all 32 consecutive

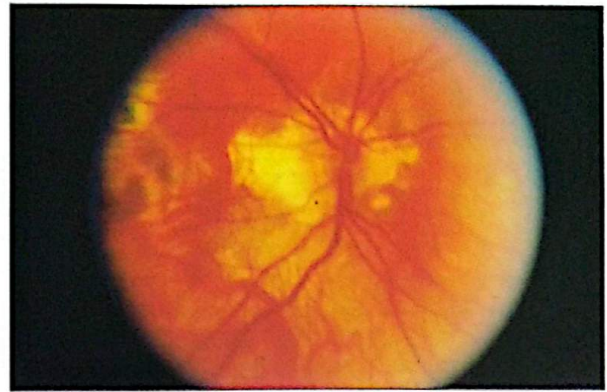


FIGURE 3.26 High myopia with typical peripapillary atrophy. Stretched thin vessels and compromised circulation often lead to macular degeneration. (Courtesy Dr. C. W. Yung, Indiana University.)

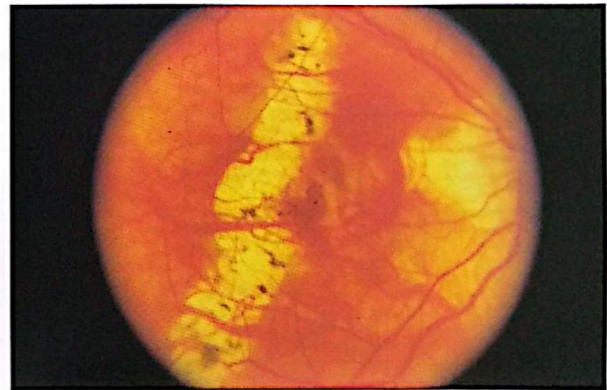


FIGURE 3.27 Same patient with a chorioretinal atrophy in the temporal macular region. (Courtesy Dr. C. W. Yung, Indiana University.)

patients with acute or chronic recurrent central serous chorioretinopathy showed a localized delay in choroidal arterial filling followed by choroidal hyperperfusion in the area of the damaged RPE (Prunte, Flammer, 1996). These changes corresponded to areas with pigment epithelial detachment or focal leakage from the RPE found in fluorescein angiography. The authors speculate that capillary or venous congestion after ischemia in one or more choroidal lobules might be the reason for the choroidal hyperpermeability associated with central serous chorioretinopathy (Prunte, Flammer, 1996).

CENTRAL SEROUS RETINOPATHY



FIGURE 3.28 Right eye, color fundus photo of a patient with central serous retinopathy.

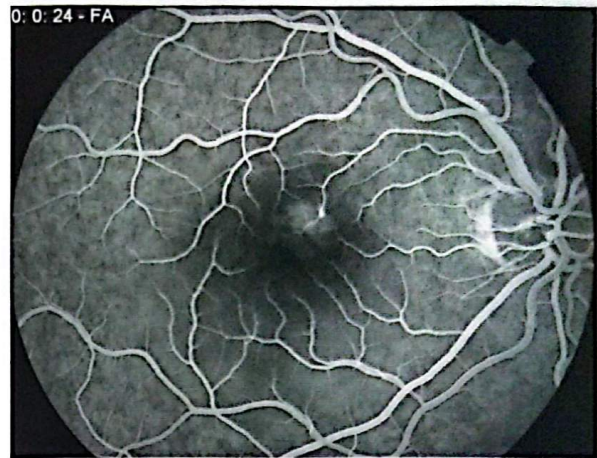


FIGURE 3.30 Fluorescein angiogram, 24" frame, showing classic central serous chorioretinopathy with one or more focal leaks at the level of the RPE. In this case, the fluorescein enters into the exudative retinal detachment, indentifying one point.



FIGURE 3.29 Same patient, left eye, color fundus photo.



FIGURE 3.31 Same patient, frames 2'16", 5'37", and 12'1". Classic "smokestack" appearance of the fluorescein leak (seen only in 10% to 15% of cases).

MACULAR HOLE

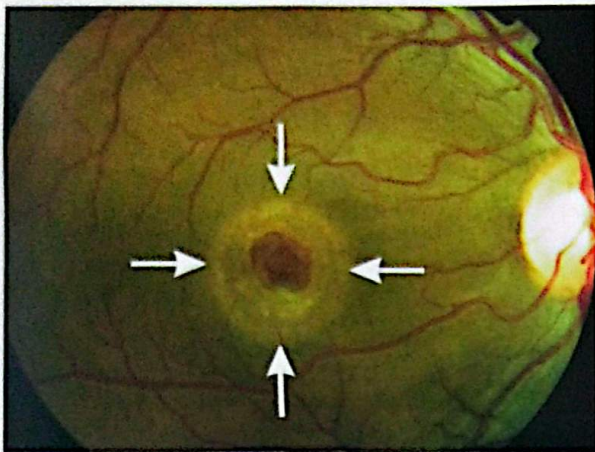


FIGURE 3.32 Right eye, color fundus photo showing chronic full-thickness macular hole. Note the central full-thickness retinal dehiscence, which is circular and measures approximately 750 μm . A surrounding cuff of subretinal fluid is present (*arrows*). The large size of this hole is consistent with the chronic full-thickness macular hole. There can also be associated pigmented demarcation lines at peripheral edge of the cuff of subretinal fluid (not shown here).

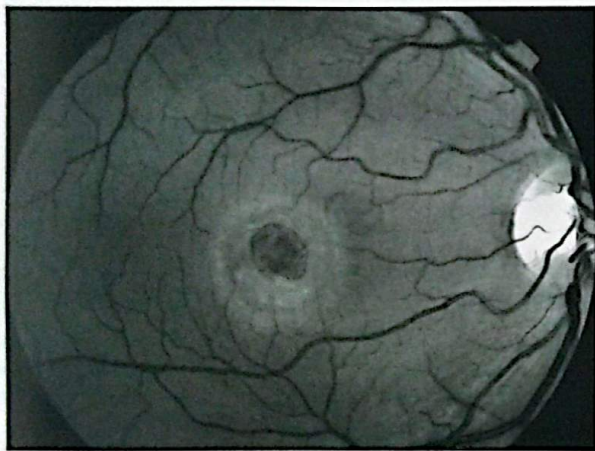


FIGURE 3.33 Red-free image from the same patient. The red-free image confirms the findings from the color fundus photo.

PRESUMED OCULAR HISTOPLASMOSIS SYNDROME

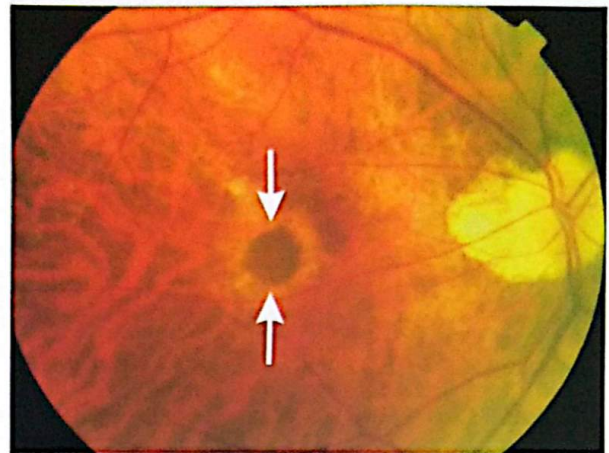


FIGURE 3.34 Right eye, color fundus photo of presumed ocular histoplasmosis syndrome (POHS). Note the peripapillary atrophy, as well as the 700 μm subretinal pigment clumping just inferior-temporal to the fovea associated with some RPE atrophy (*arrows*). The peripapillary atrophy is typical for POHS, and the inferior-temporal subretinal pigment clumping suggests a CNVM, which is also commonly encountered in this syndrome.

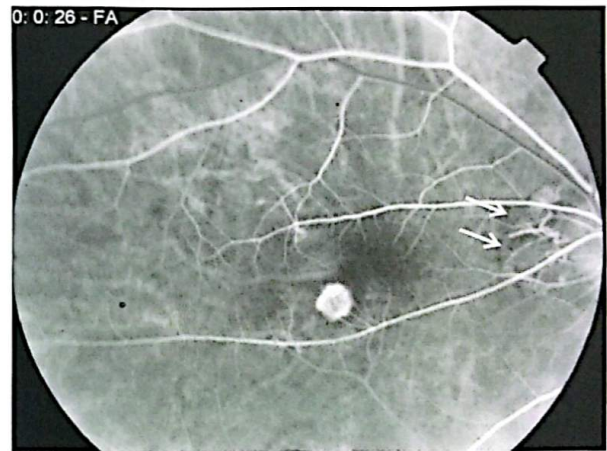


FIGURE 3.35 Frame, 26", from the early laminar venous phase. The well-defined, discrete 600- μm circular hyperfluorescence just inferior-temporal to the foveal center, consistent with a CNVM. Note the peripapillary atrophy through which the underlying choroidal vessels (*arrows*) can be seen.

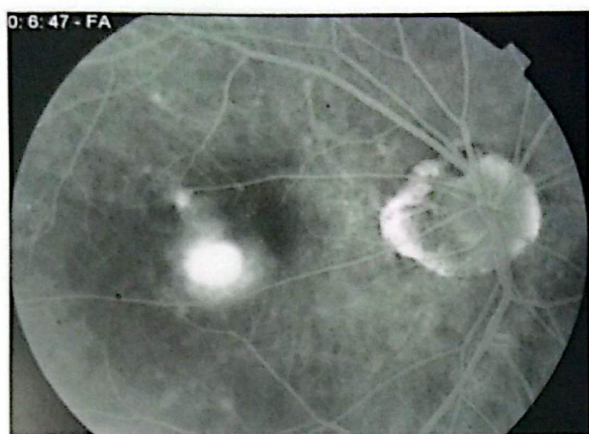


FIGURE 3.36 Same patient, 6'47" frame. The late frame of the angiogram reveals significant leakage from the inferior-temporal lesion, confirming the presence of a CNVM. There is also staining of the peripapillary atrophy, as typically encountered.

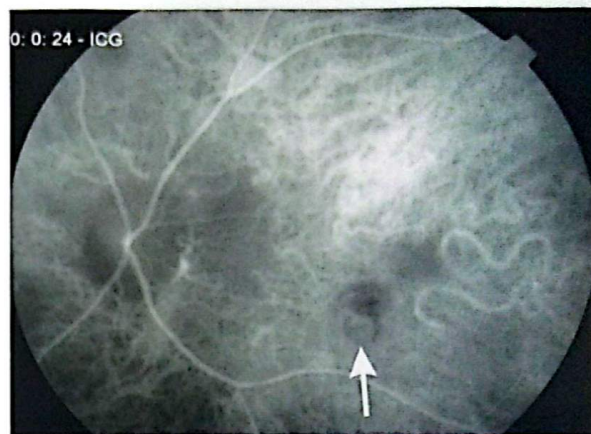


FIGURE 3.39 Same patient, ICG angiogram, 24". This post-transit frame highlights both the retinal and choroidal vasculature. An early hyperfluorescent plaque originates from the punched out spot inferior-nasal to the fovea (arrow).

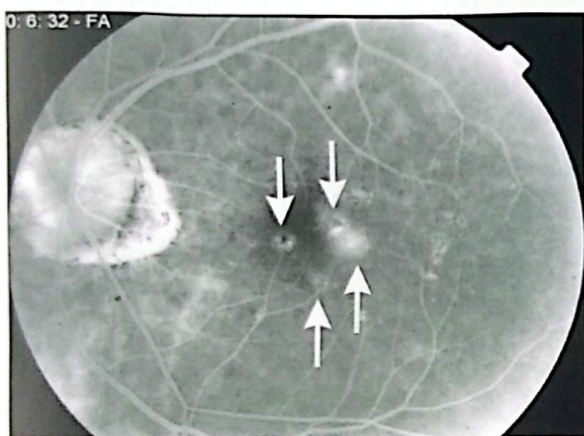


FIGURE 3.37 Same patient, 6'32" frame. The late frame of the angiogram from the left eye also reveals staining of the peripapillary atrophy, as well as staining of some "histo spots" (arrows).

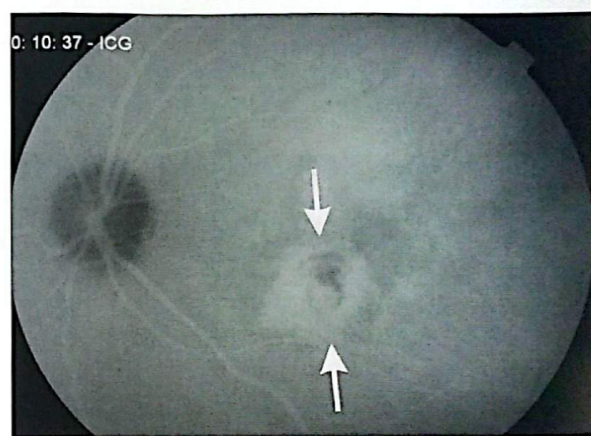


FIGURE 3.40 Same patient, 10'37" frame. The late phase of the ICG angiogram shows a 1 disc area hyperfluorescent plaque inferior-nasal to the fovea. Note that the disc is hypofluorescent, which is characteristic of a late-phase ICG angiogram.



FIGURE 3.38 POHS with choroidal neovascularization and subfoveal hemorrhage. Note the punched out lesion (arrow) inferior-nasal to the fovea associated with surrounding subretinal pigmentation, suggesting a CNVM. Outlining this lesion is a subretinal hemorrhage, originating from the CNVM.

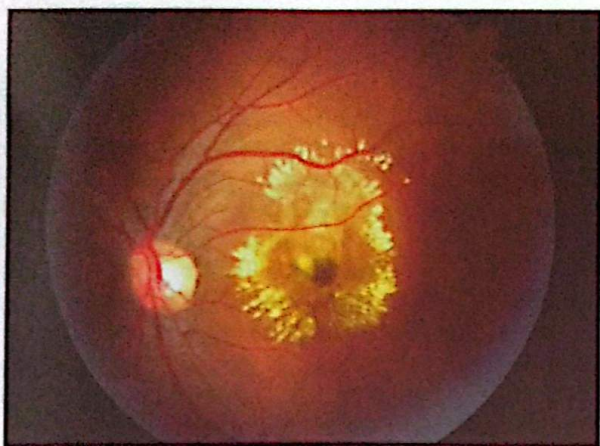


FIGURE 3.41 Left eye, color fundus photo of POHS. Note the prominent hard exudates, typical for chronic subretinal fluid. (Courtesy Dr. C. W. Yung, Indiana University.)

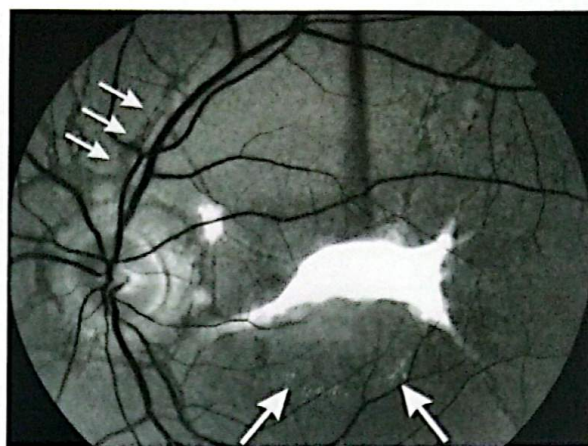


FIGURE 3.44 Red-free image of the same patient. The red-free image highlights the angioid streaks (*small arrows*). Also present is a crescent of hard exudates inferior to the subfoveal fibrosis, which demarcates the edge of some shallow subretinal fluid (*large arrows*).

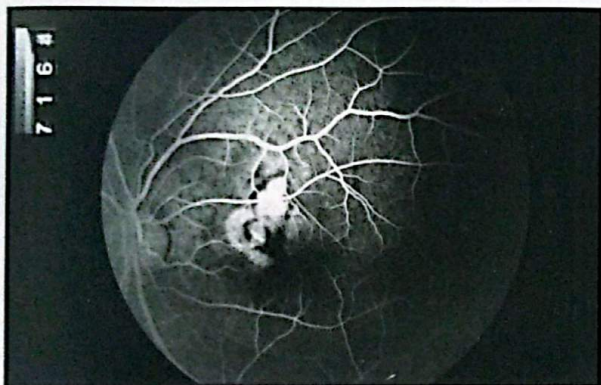


FIGURE 3.42 Same eye, fluorescein angiography. Note the well defined CNVM. (Courtesy Dr. C. W. Yung, Indiana University.)



FIGURE 3.45 Same patient, fluorescence angiogram of the left eye, 1'35" frame. The posttransit frame of the angiogram shows staining of the angioid streaks in both the peripapillary region and the perifoveal region. There is also staining of the subretinal fibrosis, as expected.

ANGIOID STREAKS

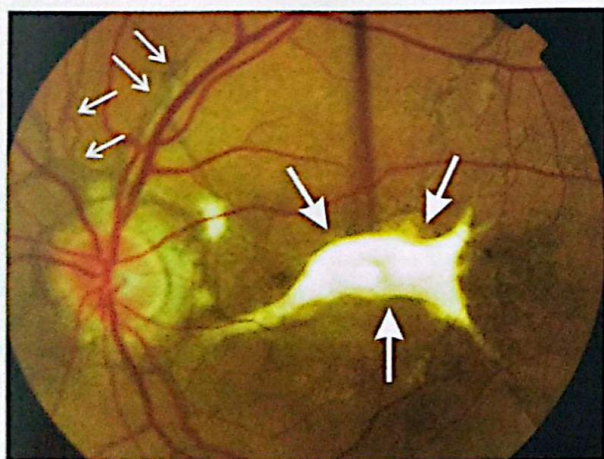


FIGURE 3.43 Left eye, color fundus photo showing angioid streaks, subfoveal fibrosis, and scarring caused by a prior CNVM. Note the linear dark lesions emanating from the optic nerve (*small arrows*), somewhat reminiscent of blood vessels for which this entity is named. A collection of subfoveal fibrosis (*large arrows*) represents scarring caused by prior subchoroidal neovascularization.

STARGARDT'S DISEASE

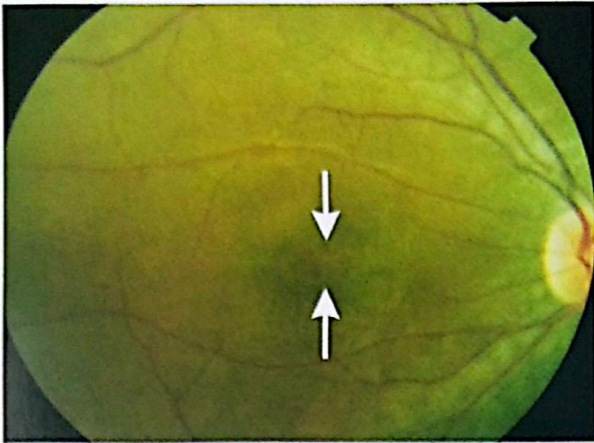


FIGURE 3.46 Right eye, color fundus photo showing Stargardt's disease. Note the RPE attenuation diffusely as "beaten bronze" appearance (arrows) in the center.



FIGURE 3.47 Same patient, fluorescein angiogram, 18" frame. The arterial phase of the angiogram reveals staining of the RPE mottling centrally.

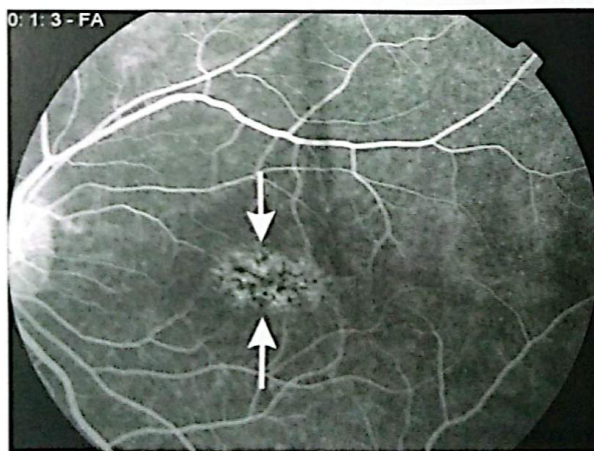


FIGURE 3.48 Same patient, left eye, 13" angiogram frame. The posttransit frame on the left reveals similar staining of the RPE mottling (arrows).

Common Retinal Vasculopathies

In central retinal artery occlusions, color Doppler imaging has demonstrated absence of blood flow in the central retinal artery, with return of flow within 1 week after the occlusion (Williamson, Baxter, Dutton, 1993). In central retinal vein occlusion, patients show reduced mean peak velocities in the central retinal vein of the affected eye compared with the fellow eye (Williamson, Baxter, 1994). In one study, patients with the ischemic central retinal vein occlusions showed additional reduction in mean peak velocities; further, color Doppler imaging of the central retinal vein was found to yield values predictive of rubeosis (Williamson, Baxter, 1994).

The ocular ischemic syndrome can result from severe carotid stenosis or ophthalmic artery occlusion (Lieb, Flaharty, Sergott, et al., 1991). In carotid stenosis, color Doppler imaging shows reduced blood velocities in the ophthalmic and central retinal arteries in proportion to the severity of the stenosis. In severe stenosis, reversal of flow in the ophthalmic artery is seen, indicating collateral perfusion via the external carotid artery. In contrast, ophthalmic artery stenosis causes high flow velocities in the ophthalmic artery.

In superior ophthalmic venous thrombosis, color Doppler imaging reveals absent flow in a dilated superior ophthalmic vein with flow through dilated collateral veins (Flaharty, Phillips, Sergott, Stefanyszyn, Bosley, Savino, 1991).

HYPERTENSIVE RETINOPATHY

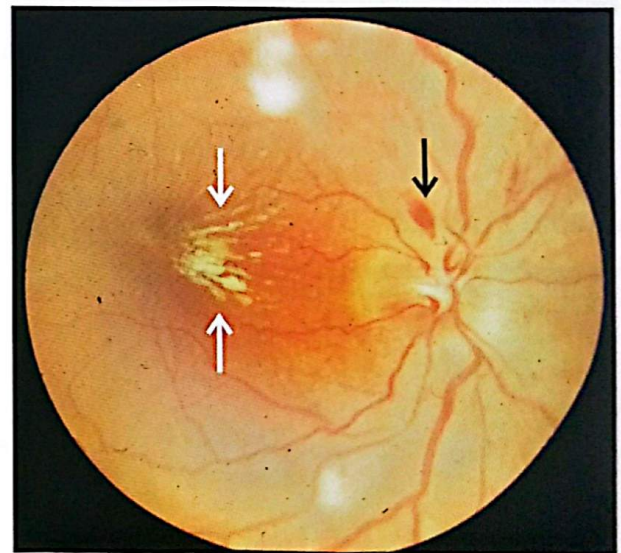


FIGURE 3.49 Hypertensive retinopathy: ischemic retinal edema, hard perimacular exudates (white arrows), splinter hemorrhage (black arrows), and papilledema.

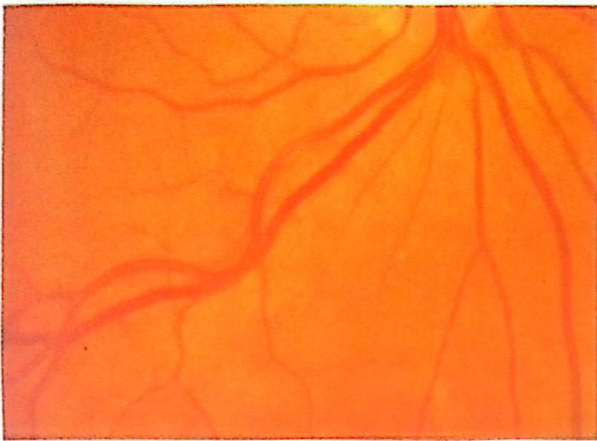


FIGURE 3.50 Hypertensive retinopathy. Note the marked changes in the lumen of the lower temporal artery.

DIABETIC RETINOPATHY

Retinal Blood Flow in Diabetes

Blood flow parameters are altered by acute and subacute changes in glucose levels. In patients with insulin-dependent diabetes mellitus, those without retinopathy who were subjected to acute elevations of glucose for as little as 1 hour had a decrease of retinal blood flow compared with nondiabetics (Bursell, Clermont, Kinsley, Simonson, Aiello, Wolpert, 1996). In keeping with the immediate retinal perfusion reduction seen during acute hyperglycemia, decreased total retinal blood flow in diabetics without diabetic retinopathy has been demonstrated (Bursell, Clermont, Kinsley, Simonson, Aiello, Wolpert, 1996; Arend, Remky, Harris, Bertram, Reim, Wolf, 1995). However, as the disease progresses, before vasoproliferation, bulk retinal blood flow is typically found to be above normal (Blair, Feke, Morales-Stoppello, et al., 1982; Cunha-Vaz, Fonseca, de Abreu, Lima, 1978; Kohner, Hamilton, Suanders, Sutcliffe, Bulpitt, 1975; Yoshida, Feke, Green, et al., 1983). This result has been confirmed in studies utilizing both laser Doppler flowmetry and video fluorescein angiography (Cunha-Vaz, Fonseca, de Abreu, Lima, 1978; Kohner, Hamilton, Suanders, Sutcliffe, Bulpitt, 1975; Grunwald, Brucker, Grunwald, Riva, 1993; Grunwald, Riva, Sinclair, Brucker, Petrig, 1986). In some studies, in the advanced stages of nonproliferative retinopathy, a strong correlation exists between elevation in blood flow and degree of retinopathy (Clermont, Aiello, Mori, Aiello, Bursell, 1997). The rise in total retinal perfusion during preproliferative retinopathy presumably arises from thickening of the capillary basement membrane, secondary to elevated diacylglycerol and protein kinase C levels, leading to occlusive angiopathy and tissue hypoxia that increases bulk blood flow demands (Kohner, Patel, Rassam, 1995; Dahl-Jorgensen, 1998;

Berkowitz, Kowluru, Frank, Kern, Hohman, Prakash, 1999).

Abnormal Retinal Blood Flow Autoregulation in Diabetes

In patients with diabetes the retina's inability to vasoconstrict in response to increased arterial blood oxygen content is one of several lines of evidence showing that the diseased retina lacks normal autoregulatory responsiveness. Diabetics suffer from retinal autoregulatory incapacity in proportion to disease severity. For example, when intravenous tyramine administration is used to elevate mean arterial pressure, a 35% pressure rise is required to increase bulk retinal flow in healthy persons (Rassam, Patel, Kohner, 1995). In normoglycemic diabetics, a 25% pressure elevation increased retinal flow; only a 15% rise in pressure was required to increase retinal perfusion in hyperglycemic diabetic patients (Rassam, Patel, Kohner, 1995). Similarly, the beta-adrenergic sensitivity of the ocular vessels of diabetics is lower than that of control subjects (Schmetterer, Findl, Strenn, et al., 1997). Further, using the blue light entopic phenomenon, investigators have demonstrated faulty retinal capillary autoregulation in response to both isocapnic hypoxia and to intraocular pressure elevation (Fallon, Maxwell, Kohner, 1987; Sinclair, Grunwald, Riva, Braunstein, Nichols, Schwartz, 1982).

Retinal Capillary Perfusion in Diabetes

Progression of diabetes is associated with loss of perifoveal capillaries (Arend, Remky, Harris, Bertram, Reim, Wolf, 1995; Fallon, Chowienczyk, Kohner, 1986; Rimmer, Fallon, Kohner, 1989; Sinclair, 1991). The perifoveal intercapillary area and foveal avascular zone are significantly larger in diabetic patients than in healthy people (Arend, Remky, Harris, Bertram, Reim, Wolf, 1995; Arend, Wolf, Harris, Reim, 1995; Arend, Wolf, Remky, et al., 1994). In addition, these avascular areas are larger in diabetic patients with decreased visual acuity (Arend, Remky, Harris, Bertram, Reim, Wolf, 1995; Arend, Wolf, Harris, Reim, 1995). This process occurs at the earliest stages of the disease, since sensitive tests of visual acuity find reductions proportional to capillary loss in patients with very mild retinopathy (Arend, Remky, Evans, Stuber, Harris, 1997).

Effects of Diabetes on Retrobulbar and Choroidal Vascular Regulation

Although diabetics clearly experience dysfunctional retinal perfusion, deficiencies in the retrobulbar and choroidal circulation are also apparent in this disease. Because the retina is supplied via the central retinal artery, defects in central retinal arterial hemodynamics are manifest in diabetes. Color Doppler imaging reveals decreased mean peak systolic velocity in the central retinal artery in subjects with nonproliferative diabetic

retinopathy (NPDR), as compared with subjects in a preretinopathy control group (Guyen, Ozdemir, Hasanreisoglu, 1996). Similarly, the presence of proliferative retinopathy was found to correlate strongly with reduced flow velocities in the retrobulbar vessels, most markedly in the central retinal artery (Goebel, Iach, Ho, Sergott, Farhoumand, Grehn, 1995). These changes in central retinal arterial flow velocity do not, however, necessarily reflect changes in bulk flow, and changes in the central retinal vessel as well are presumed to result from, rather than cause, changes in vasoregulation within the retina itself.

Unlike the central retinal artery, whose watershed is exclusively retinal, the ophthalmic artery nourishes the entire orbit. Nonetheless, diabetes does alter ophthalmic arterial hemodynamics. For example, hyperbaric oxygen therapy, which reduces flow velocities in the ophthalmic artery in healthy persons and in diabetics without clinically significant neuropathy, increases these velocities in patients with neuropathy (Okamoto, Nishimura, Goami, Harino, 1997). Although such results could reflect defects in autonomic or locally mediated factors that control the orbital circulation, they could also arise from widespread microvascular abnormalities throughout the retina, choroid, and other tissues within the ophthalmic watershed.

Little is known regarding the choroidal blood flow in diabetes. Total choroidal perfusion may not be altered by diabetes. This is supported by studies showing that flow velocities in the posterior ciliary arteries feeding the choroid are unchanged by the disease (Guyen, Ozdemir, Hasanreisoglu, 1996).

Effect of Laser Treatment on Blood Flow in Diabetic Retinopathy

Panretinal photocoagulation reduces both retinal and retrobulbar blood flow (Hessemmer, Schmidt, 1997; Mendivil, 1997; Mendivil, Cuartero, Mendivil, 1995; Schlotte, Schefig, Nissen, 1981). Blood flow in the ophthalmic artery and the central retinal artery and vein, are reduced for at least 2 years after photocoagulation therapy (Mendivil, 1997; Mendivil, Cuartero, 1996). Although this result may merely indicate that coagulation has reduced the extent of vascular proliferation, leakage, and aneurysm formation, evidence also shows that this therapy can upgrade retinal autoregulatory responses (Fallon, Chowienczyk, Kohner, 1986; Granwald, Riva-martin, Quint, Epstein, 1987; Mittl, Tiwari, Wilkes, 1990).

Photocoagulation therapy may in fact enhance choroidal nutrient delivery. In patients with proliferative retinopathy, choroidal oxyhemoglobin content was normalized after panretinal photocoagulation (Augsten, Komigadoff, Schwetzer, Siebel, 1997). Some authors have proposed that panretinal photocoagulation improves retinal oxygenation through the laser scar

These authors measured oxygen tensions in human patients undergoing vitreous operations for proliferative diabetic retinopathy. The oxygen tension was significantly higher ($P = .004$) over areas of retina that had been treated with panretinal photocoagulation than it was over untreated areas in the same retina, supporting the hypothesis that panretinal photocoagulation improves the oxygen supply to the inner retina and thereby minimizes the influence of retinal ischemia in diabetic retinopathy (Stefansson, Machemer, de Juan, McCuen, Peterson, 1992).



FIGURE 3.51 Right eye, color fundus photo. NPDR with clinically significant macular edema after macular edema laser treatment. Note the scattered-dot hemorrhages and microaneurysms, also note the prior macular laser treatment scars (arrows).

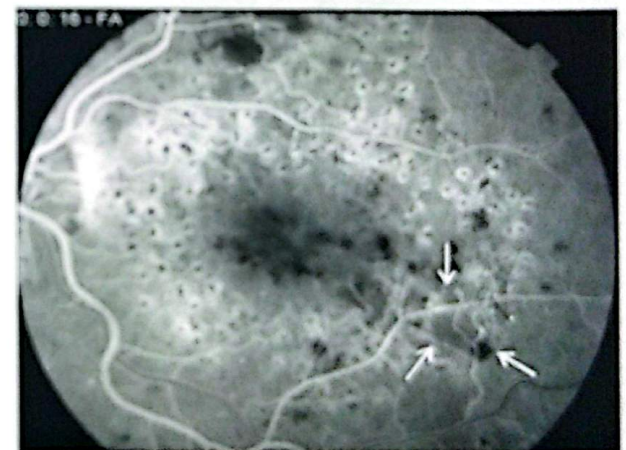


FIGURE 3.52 Same patient, left eye, 16° fluorescein angiogram frame. This frame was taken in the laminar venous flow phase. Note the scattered microaneurysms, the laser scars, which appear as central hypofluorescence with surrounding staining. Also note the 1.5 disc area region of capillary dropout inferior-temporal to the fovea (arrows).

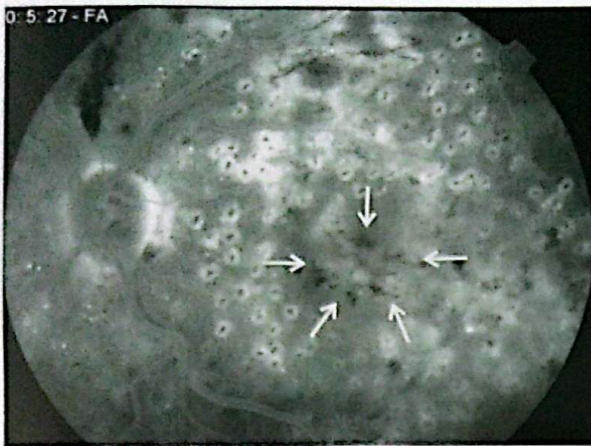


FIGURE 3.53 Same patient, 5'20" frame. The late frame of the angiogram reveals leakage inferior-temporal to the fovea and also into the fovea, forming a somewhat petaloid appearance (*arrows*) consistent with cystoid macular edema.

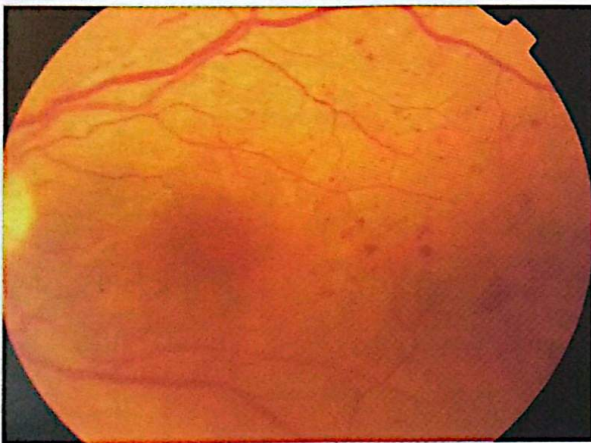


FIGURE 3.54 Color fundus photo of the left eye of another NPDR patient. (Courtesy Dr. C. W. Yung, Indiana University.)



FIGURE 3.55 Fluorescein angiogram depicts microaneurysms, most prominent superior-temporally to the fovea, as well as hypofluorescent laser scars. (Courtesy Dr. C. W. Yung, Indiana University.)



FIGURE 3.56 Right eye, color fundus photo showing proliferative diabetic retinopathy, clinically significant macular edema, and lipemia retinalis. Note the boat-shaped subhyaloid hemorrhage superior to the inferior arcade. This is suggestive of some underlying neovascularization from proliferative diabetic retinopathy. Also note the severe and diffuse macular edema with very dense lipid hard exudates centrally. There is exudation of the lipids from the vessels, creating some sheathing as a result of the hyperlipidemia (*arrows*), seen in the lower left-hand corner and upper left corner of the photo.

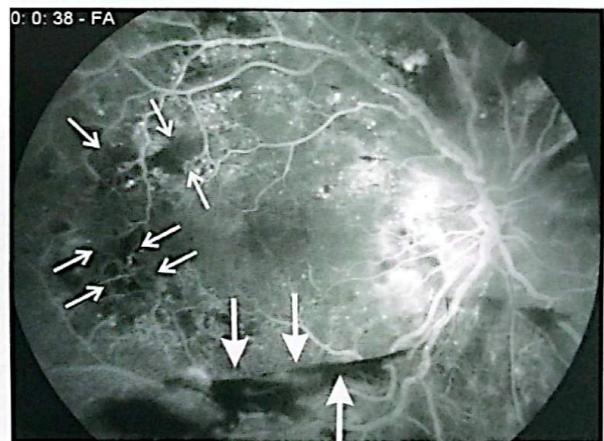


FIGURE 3.57 Same patient, 38" frame. The postlaminar venous flow phase of the angiogram reveals scattered microaneurysms and patchy capillary dropout (*small arrows*). The previously noted subhyaloid hemorrhage blocks the underlying fluorescence from the retinal and choroidal circulation (*large arrows*).

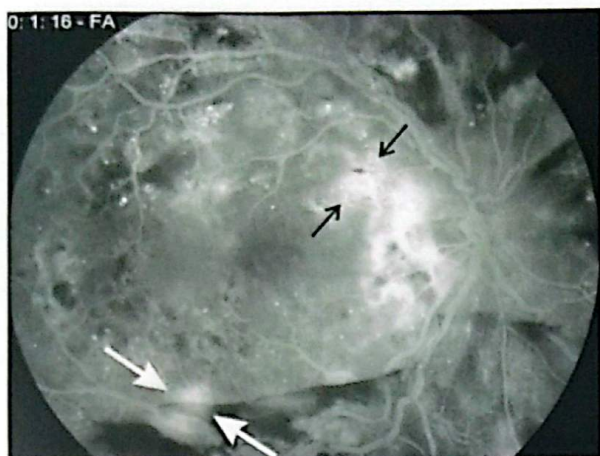


FIGURE 3.58 Frame, 1'16". The midframes of the angiogram show leakage from the microaneurysms (*small black arrows*). Also, more intense leakage at the temporal aspect of the inferior subhyaloid hemorrhage suggests neovascularization there (*large white arrows*).

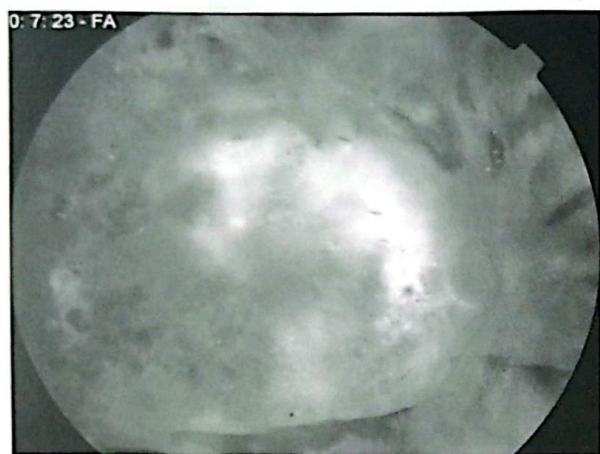


FIGURE 3.59 Frame, 7'23". The late frame of the angiogram reveals severe and diffuse leakage throughout the entire posterior pole.



FIGURE 3.60 Right eye, color fundus photo showing macular RPE changes, related to prior macular laser treatment, as well as panretinal laser treatment, noted inferiorly. (Courtesy Dr. C W. Yung, Indiana University.)

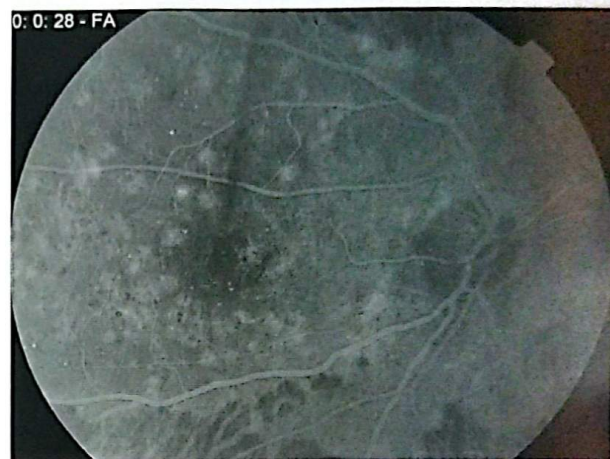


FIGURE 3.61 Same patient, early 28" frame of the fluorescein angiogram, showing staining of the laser scars. (Courtesy Dr. C. W. Yung, Indiana University.)

CENTRAL RETINAL VEIN OCCLUSION



FIGURE 3.62 Papilledema, cotton-wool spots and dilated tortuous veins, in ischemic central retinal vein occlusion.



FIGURE 3.63 Central retinal vein occlusion with characteristic diffuse retinal hemorrhages, dilated and tortuous retinal veins, as well as swollen optic nerve head.



FIGURE 3.64 Right eye, color fundus photo showing a central retinal vein occlusion with widespread retinal hemorrhages. (Courtesy Dr. C. W. Yung, Indiana University.)



FIGURE 3.65 Fluorescein angiographic image of the same eye, showing extensive hypofluorescent areas in the superior hemisphere, with severe capillary dropout superiorly. (Courtesy Dr. C. W. Yung, Indiana University.)

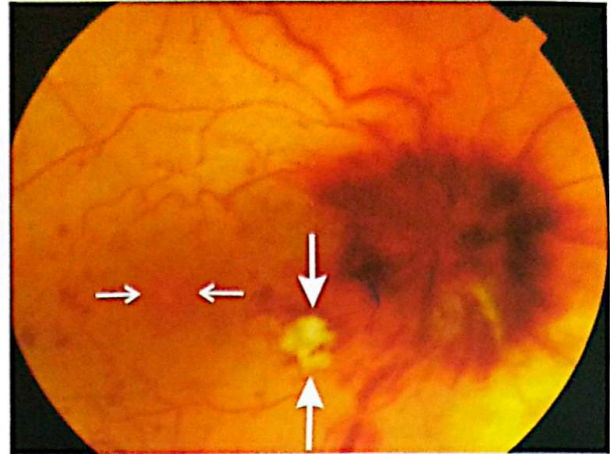


FIGURE 3.66 Right eye, color fundus photo showing central retinal vein occlusion. Note the swollen hemorrhagic disc and retinal hemorrhages that extend through the macula. There is a notable cotton-wool spot (*large arrows*) inferior-nasal to the fovea and cystoid macular edema centrally (*small arrows*). The retina is diffusely edematous.



FIGURE 3.67 Same patient, red-free photo highlighting the clinical features noted previously, especially the hemorrhages at the ONH and throughout the posterior pole.



FIGURE 3.68 Angiography frame, 26". The angiogram shows delayed filling of the retinal veins. Blockage by the retinal hemorrhage is seen clinically.

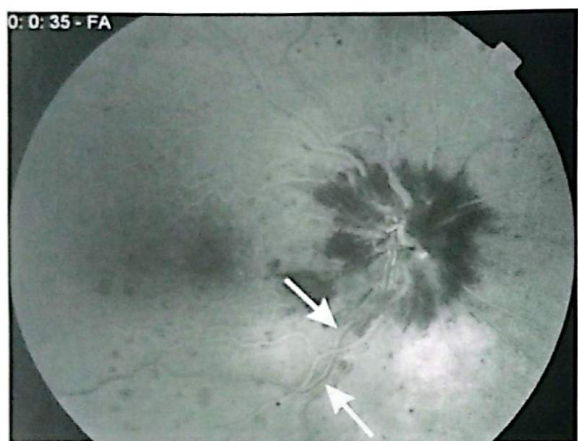


FIGURE 3.69 Same patient, 35" frame. At 35", there is early laminar venous flow in the retinal veins, which is significantly delayed (arrows).

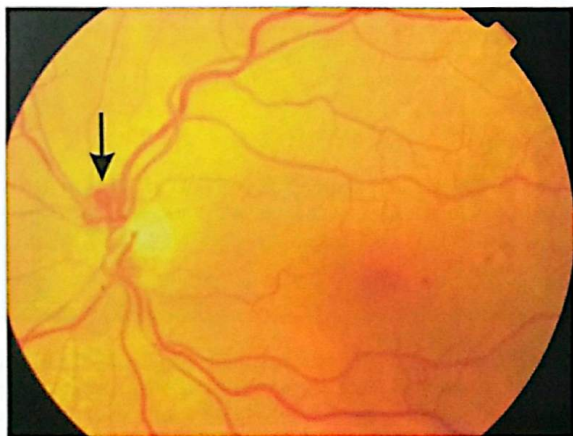


FIGURE 3.70 Left eye, color fundus photo from the same patient reveals some vascular loops (arrow) at the optic nerve head (ONH), suggesting a prior central retinal nerve occlusion.

BRANCH RETINAL VEIN OCCLUSION

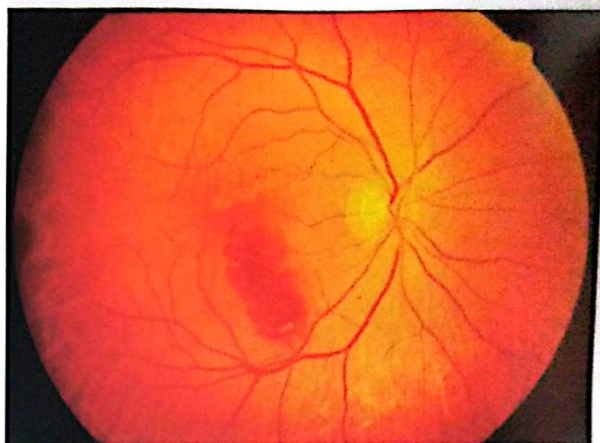


FIGURE 3.71 Branch retinal vein occlusion including the macular area with hemorrhage along the occluded inferior tributary vein.

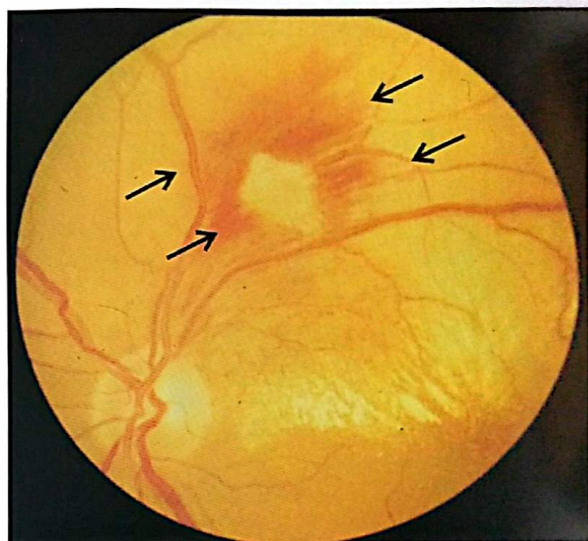


FIGURE 3.72 Superior branch retinal vein occlusion with clearing retinal hemorrhages and chronic macular edema manifested by the hard exudates.

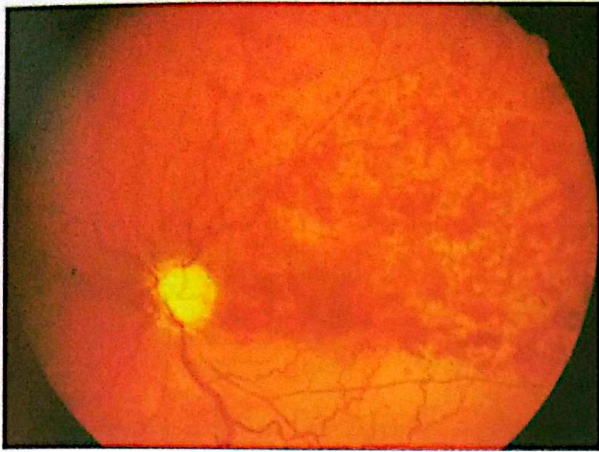


FIGURE 3.73 Branch retinal vein occlusion with massive intra-retinal and epiretinal hemorrhages superiorly.

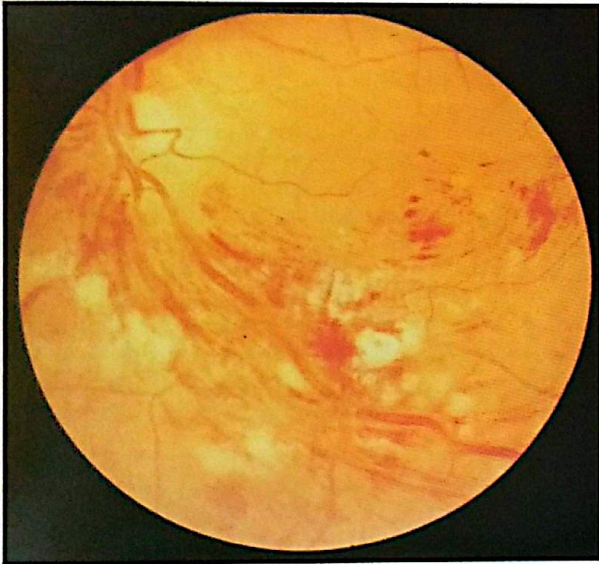


FIGURE 3.74 Ischemic branch retinal vein occlusion with hemorrhages and cotton-wool spots.

FIGURE 3.77 Same patient. The postlaminar venous flow phase of the angiography reveals significantly delayed filling of the inferior-temporal branch retinal vein (*large arrows*). Also, significant capillary dropout is noted along the proximal distribution of the inferior-temporal vein (*small arrows*). More distally, in the inferior-temporal macula, there are laser scars from prior treatment of the associated macular edema. These laser scars show central hypofluorescence with surrounding leakage

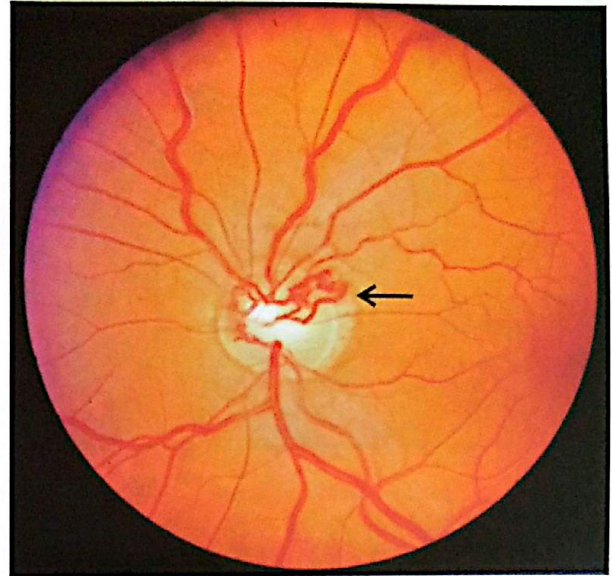
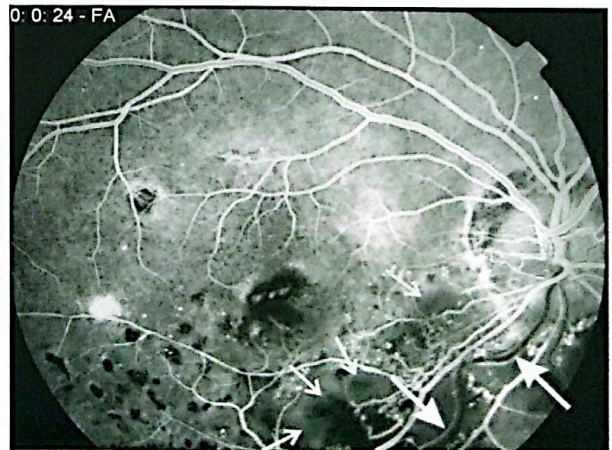


FIGURE 3.75 Cilioretinal shunt vessels after branch vein occlusion.



FIGURE 3.76 Right eye, color fundus photo showing inferior-temporal branch retinal vein occlusion with laser scars visible inferior-temporally and hemorrhages inferiorly along the inferior branch retinal vein occlusion.



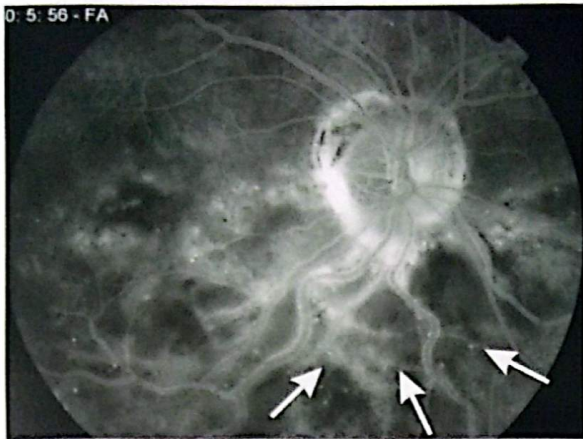


FIGURE 3.78 Same patient, 5'56'' frame. The late frame of the angiogram shows staining of the veins, consistent with prior occlusion-related endothelial injury. Also seen is hypofluorescence in the regions of capillary dropout (*arrows*). Some leakage is present as well, causing some degree of macular edema.

CENTRAL RETINAL ARTERY OCCLUSION

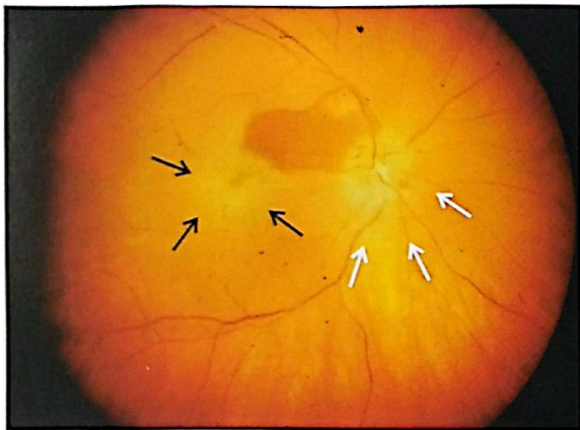


FIGURE 3.79 Right eye, color fundus photo depicting a central retinal artery occlusion with a visible embolus in the central retinal artery as it branches on the optic nerve head. Note that severely attenuated arteries (*white arrows*). Note the characteristic cherry red spot (*black arrows*), in which the normal choroidal vascular hue is visible only at the fovea, with the surrounding ischemia opaque retina obscuring the normal choroidal vascular hue extrafoveally. In addition, this particular case also depicts sparing of a ciliary retinal artery, which emerges from the choroidal circulation and runs temporally from the optic nerve head along the maculo-papillary bundle with preservation of the retinal circulation along its course.

BRANCH RETINAL ARTERY OCCLUSION

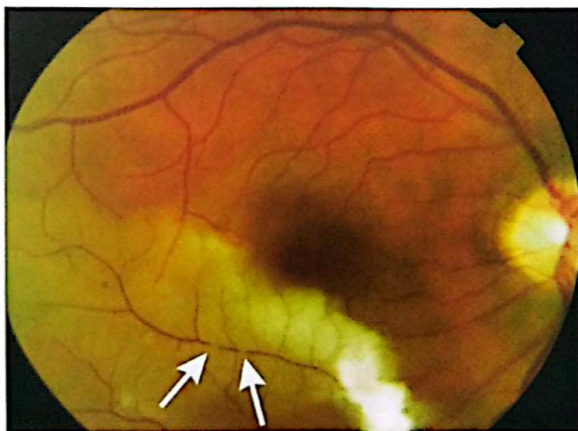


FIGURE 3.80 Tributary branch retinal artery occlusion. Note the opacified, whitened, and ischemic retina in the inferior temporal macula along the distribution of a branch retinal artery. The artery also shows platelet fibrin emboli (*arrows*).

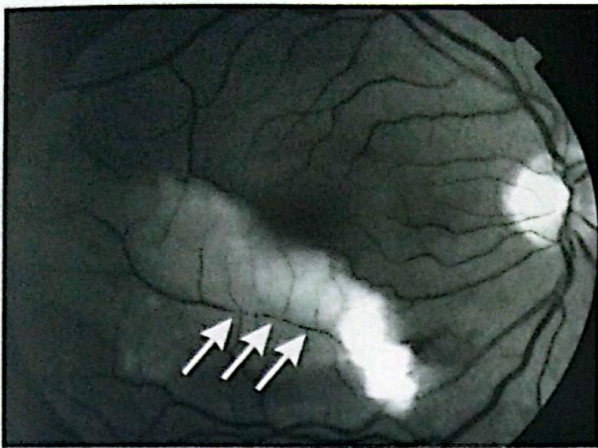


FIGURE 3.81 Same patient, red-free image. The red-free photo highlights these features well. The emboli are readily noted within the lumina of the arteries (*arrows*).



FIGURE 3.84 Branch retinal artery occlusion of the right eye in the superior-temporal arcade. Note the prominent edema surrounding the vessel. (Courtesy Dr. C. W. Yung, Indiana University.)

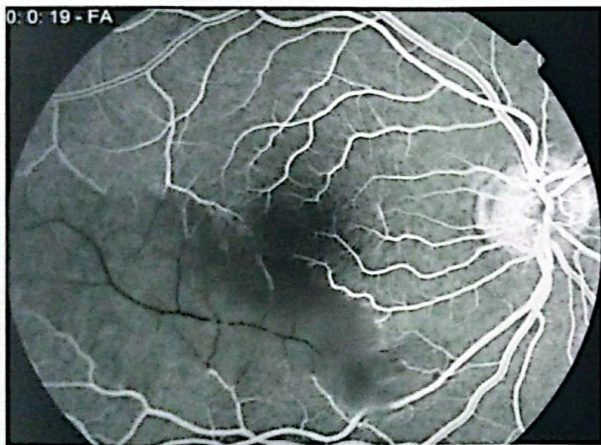


FIGURE 3.82 Same patient, 19" angiogram frame. The post-laminar venous flow frame of the angiogram reveals nonperfusion of the branch retinal artery and associated retinal capillaries.

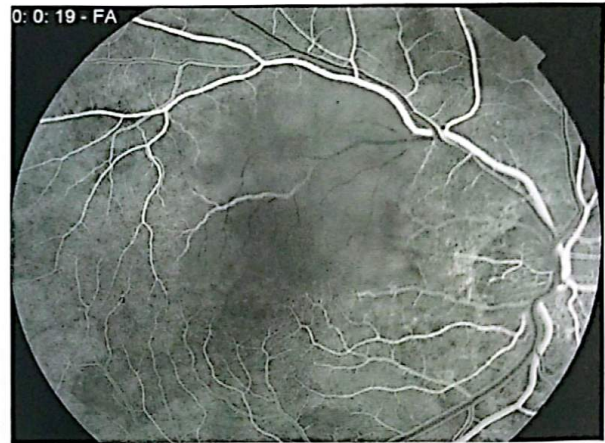


FIGURE 3.85 Angiogram of the same eye depicts an ischemic hypofluorescent region surrounding the nonperfused branch retinal artery. (Courtesy Dr. C. W. Yung, Indiana University.)

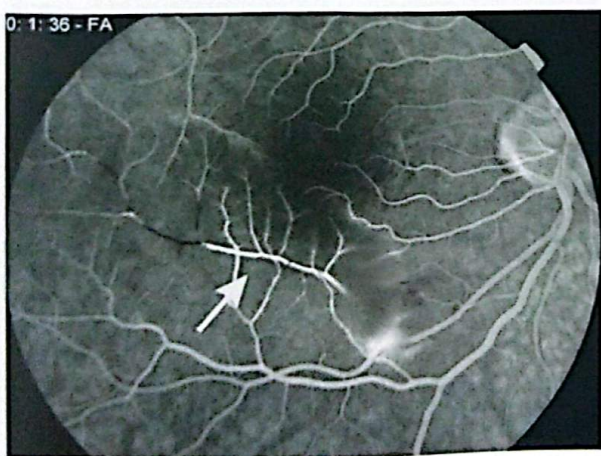


FIGURE 3.83 Same eye, 1'36" frame. The later frames of this angiogram show very slow and abnormal filling of the occluded branch retinal artery (*arrow*). Branch retinal artery occlusions can be complete or incomplete. Typically, cholesterol emboli do not cause complete occlusions, whereas platelet fibrin emboli cause more complete occlusions.



FIGURE 3.86 Branch retinal arterial occlusion: the ischemic pale retina surrounds the occluded vessel.

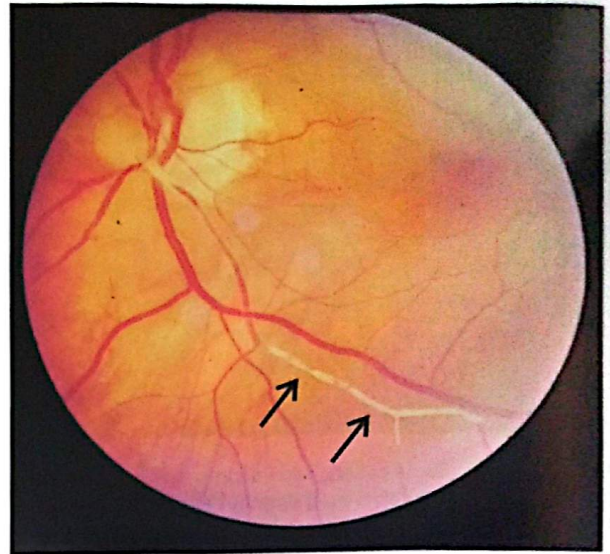


FIGURE 3.88 Occlusion of inferior temporal retinal artery (*black arrows: obliterated vessel*).

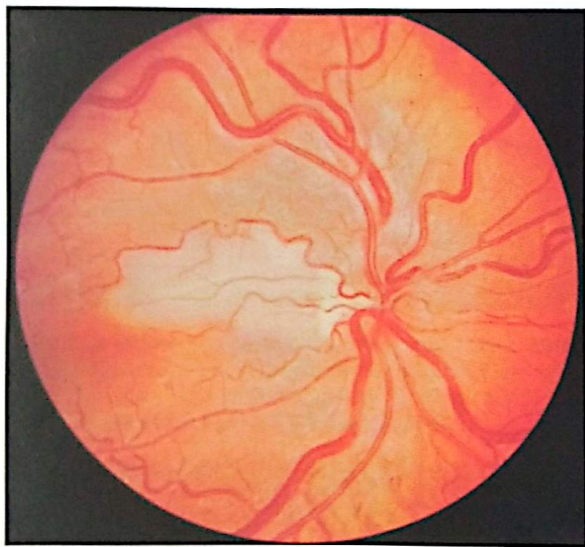


FIGURE 3.87 Branch artery occlusion of the cilioretinal artery with surrounding ischemic pale retina.

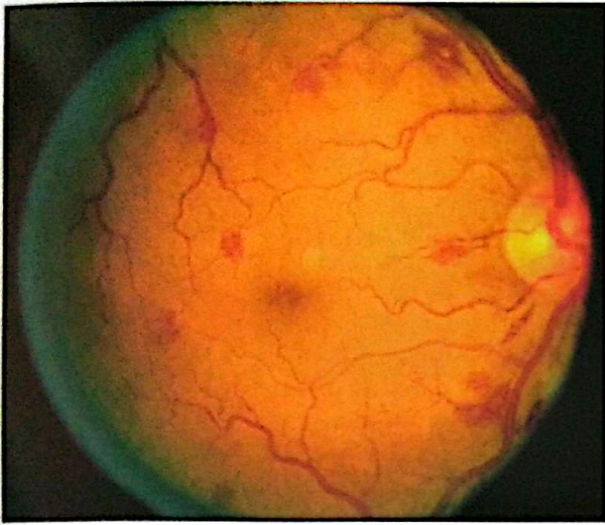
LEUKEMIA

FIGURE 3.89 Note the white centered retinal hemorrhages, known as roth spots. (Courtesy Dr. C. W. Yung, Indiana University.)

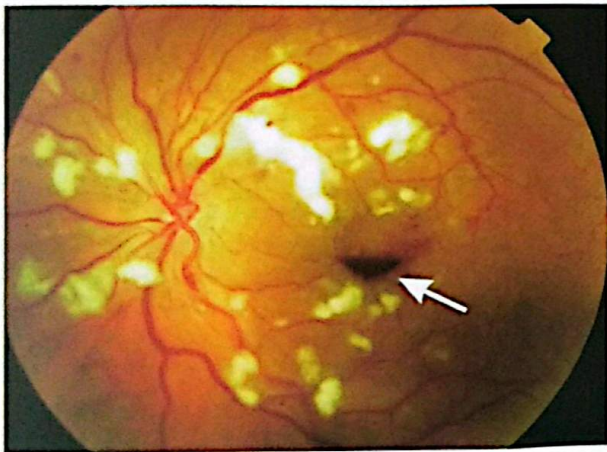
VASCULITIS

FIGURE 3.90 Left eye, color fundus photo. Vasculitis caused by systemic lupus erythematosus. Note the diffuse cotton-wool spots and retinal hemorrhages typical of this vasculitis process, which has led to some ischemia. Also seen is a small boat-shaped subhyaloid hemorrhage in the foveal region (*arrow*).

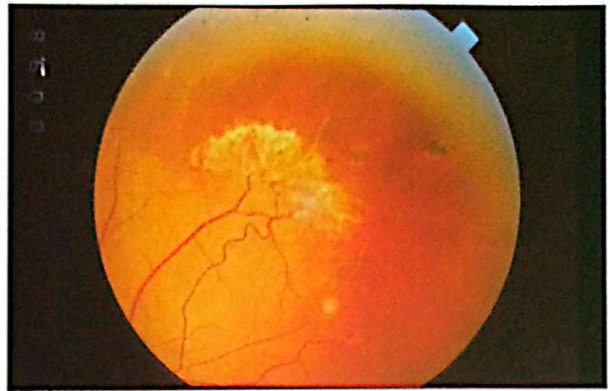
SICKLE CELL ANEMIA

FIGURE 3.91 Sickle cell anemia with presence of neovascularization and more peripheral featureless ischemic retina containing some ghost vessels. (Courtesy Dr. C. W. Yung, Indiana University.)

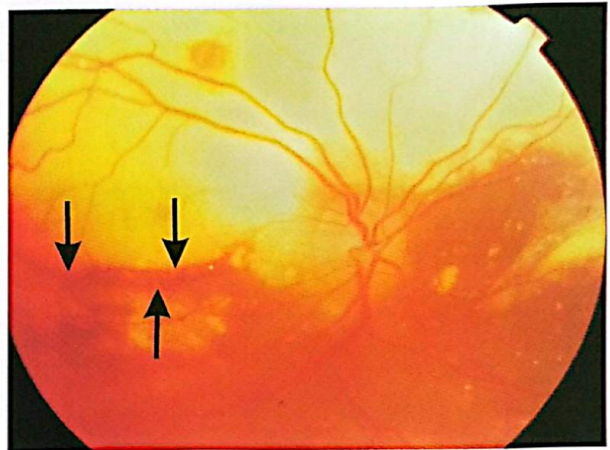
COATS' DISEASE

FIGURE 3.92 Right color fundus photo showing Coats' disease. Note the massive subretinal exudation throughout the superior macula. Note the dilated and telangiectatic vessels in the macular region (*arrows*).

RETINITIS PIGMENTOSA

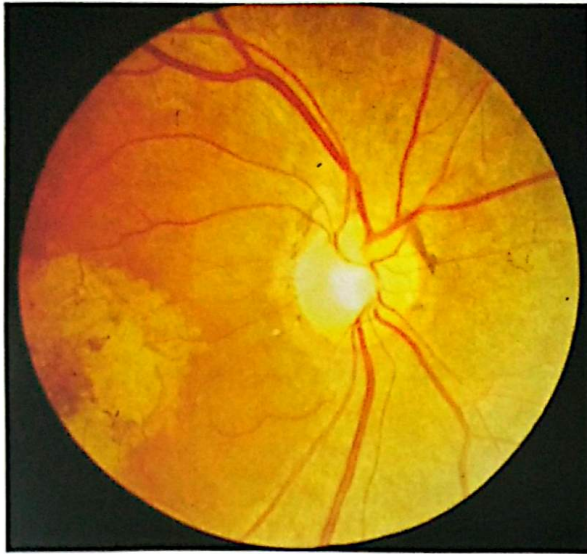


FIGURE 3.93 Retinitis pigmentosa with some waxy pallor of the optic nerve head, attenuated arteries, and diffuse RPE atrophy and mottling. The attenuation of the vessels in retinitis pigmentosa is thought to be secondary to the decreased metabolic demands of the compromised retina. (Courtesy Dr. C. W. Yung, Indiana University.)



FIGURE 3.94 Retinitis pigmentosa: typical pigmentation in the periphery and attenuated vessels. (Courtesy Dr. C. W. Yung, Indiana University.)

HUMAN IMMUNODEFICIENCY VIRUS

Several investigators speculate that in patients with human immunodeficiency virus (HIV), altered hemodynamics lead to retinopathy because it shares many features of other retinal vascular diseases, such as diabetic and hypertensive retinopathy. On fluorescein angiography, patients with HIV retinopathy display microaneurysms, telangiectatic vessels, and capillary nonperfusion (Holland, Pepose, Pettit, Gottlieb, Yee, Foos, 1983; Freeman, Lerner, Mines, 1984; Newsome, Green, Miller, et al., 1984; Pepose, Holland, Nestor, Cochran, Foos, 1985; Jabs, Green, Fox, Polk, Bartlett, 1989). Histopathologic findings show these patients to have features typical of diabetic retinopathy, including loss of pericytes, swollen endothelial cells, thickened basement membranes, and narrowed capillary lumens (Freeman, Lerner, Mines, 1984; Newsome, Green, Miller, et al., 1984; Pepose, Holland, Nestor, Cochran, Foos, 1985; Glaslow, Weisberger, 1994).

Using fluorescein with scanning laser ophthalmoscopy and digital image processing technology, direct objective measurement of retinal blood flow in these patients is possible. In one recent study, arteriovenous passage (AVP) time to assess the macrocirculation and perifoveal capillary blood flow velocity (CFV) to assess the microcirculation were measured in 23 HIV-infected patients and 23 control subjects (Yung, Harris, Massicotte, 1996). No significant difference was seen in AVP time between HIV-positive patients and the control group. However, a significant decrease was noted in the perifoveal CFV between the HIV-infected patients and the control group. The authors speculate that a decrease in CFV, which is also seen in patients with diabetic retinopathy, may lead to ischemia and subsequent ischemia-related retinal changes found in HIV retinopathy, diabetic retinopathy, and hypertensive retinopathy.

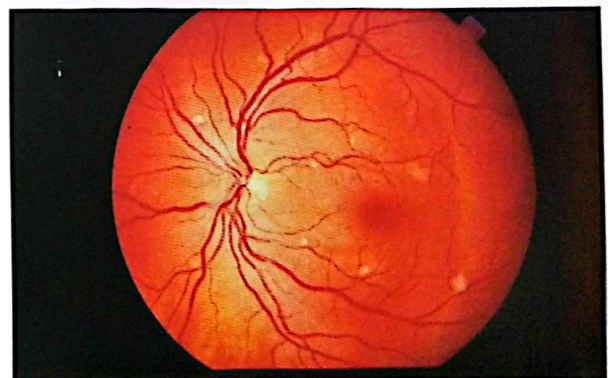


FIGURE 3.95 Left eye, color fundus photo of HIV retinopathy, characterized by cotton-wool spots, intraretinal hemorrhages, and microaneurysms. (Courtesy Dr. W. Yung.)

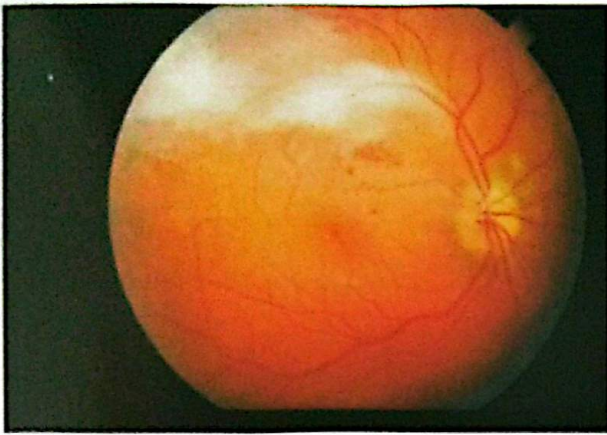


FIGURE 3.96 Advanced cytomegalovirus retinitis in an AIDS patient. Note the active white retinitis and surrounding associated hemorrhages. (Courtesy Dr. W. Yung.)

Common Optic Neuropathies

GLAUCOMA

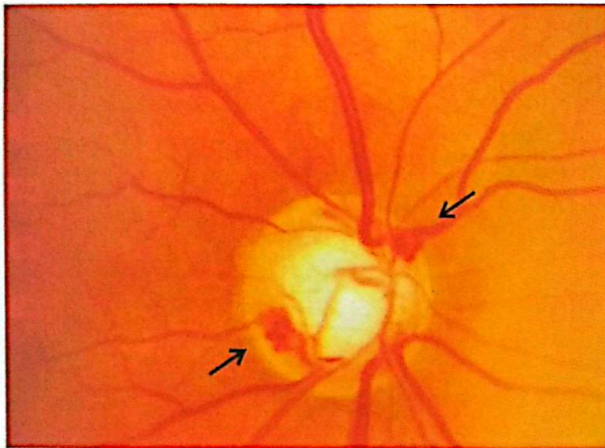


FIGURE 3.97 Marked venous dilation in glaucoma at the neuroretinal rim (arrows at the 1 and 8 o'clock positions).



FIGURE 3.99 Splinter hemorrhage in glaucoma (arrow).

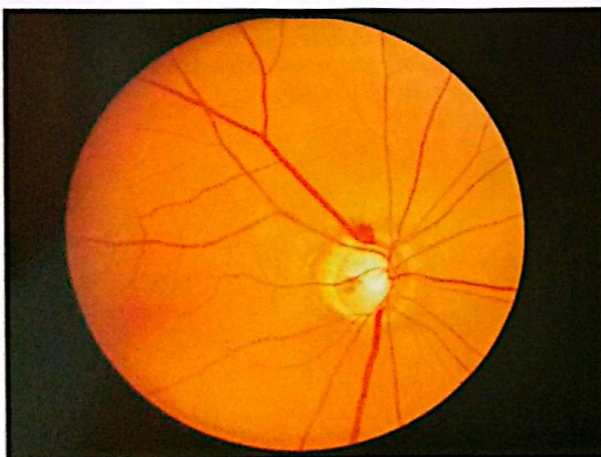


FIGURE 3.98 Intrapapillary hemorrhage (9 o'clock) and splinter hemorrhage (12 o'clock position).

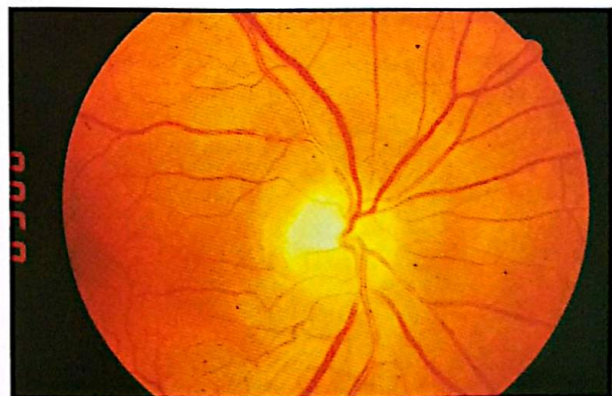


FIGURE 3.100 Focal ischemic pallor of the disc (upper temporal quadrant).



FIGURE 3.101 Sectorial optic disc pallor (upper pole of disc).

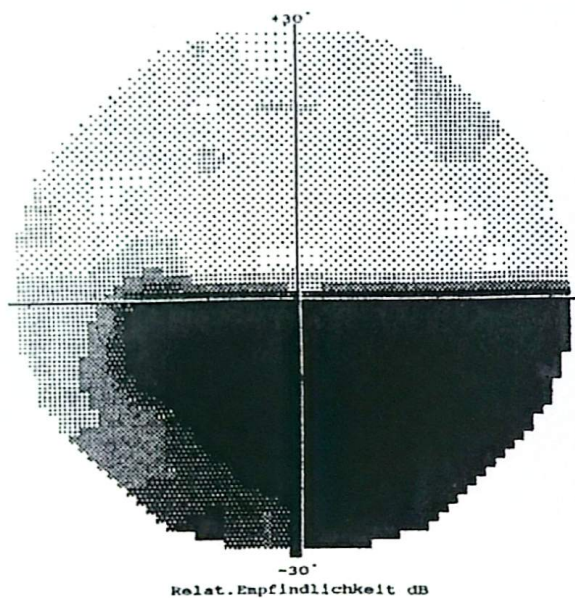


FIGURE 3.102 Corresponding visual field of Figure 3.103, showing complete loss of lower hemifield.

ATROPHY

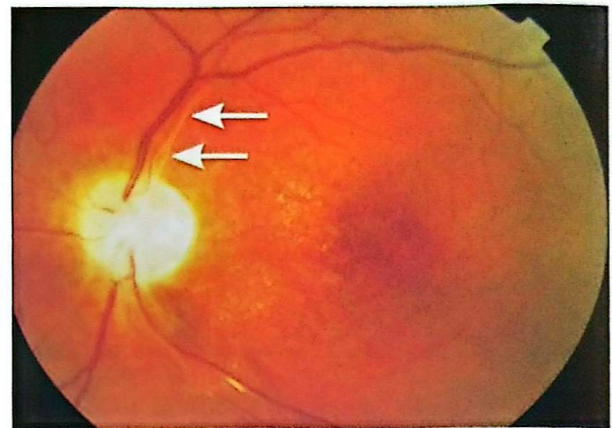


FIGURE 3.103 Left eye, color fundus photo showing optic nerve atrophy. Note the severe optic disc pallor. There is also attenuation of the retinal arteries and some vascular sheathing (arrows).

ANTERIOR ISCHEMIC OPTIC NEUROPATHY



FIGURE 3.104 Acute ischemic papilledema (acute anterior ischemic optic neuropathy [AION]).

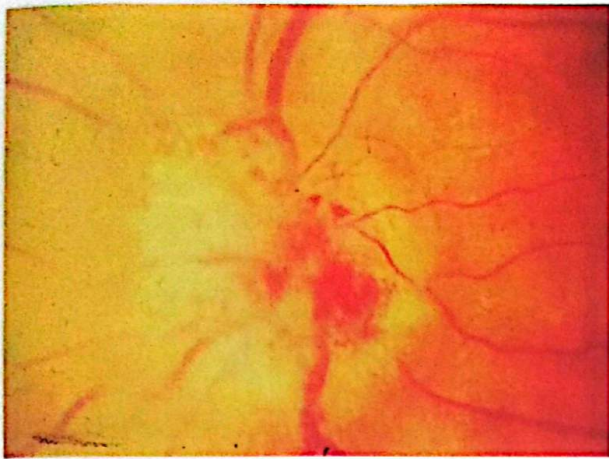


FIGURE 3.105 Massive pale papilledema in acute AION.



FIGURE 3.106 Fluorescein angiography, 7"36" frame showing ischemic optic neuropathy. This patient, who presented with a sudden visual field defect, was found to have a swollen optic disc superiorly in the left. The late frame of the fluorescein angiogram reveals sectorial leakage at the disc superiorly. This sectorial swelling and leakage of the ONH is typical of ischemic optic neuropathy and leads to altitudinal field defects. These sectorial defects result from the distribution of the vasculature to the ONH.

PAPILLEDEMA

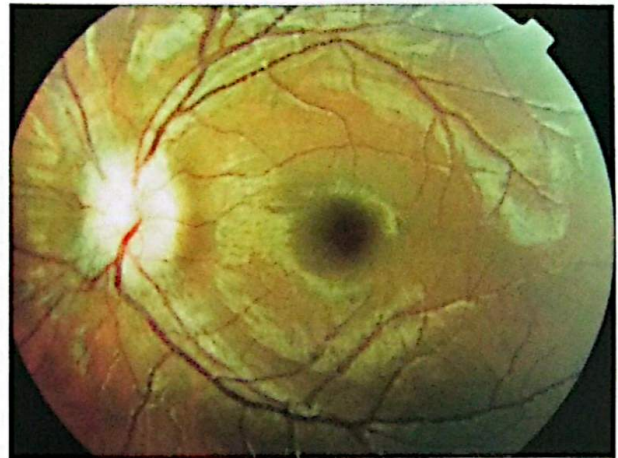


FIGURE 3.107 Left eye, color fundus photo showing papilledema. Note the swollen nerve fiber layer surrounding the disc, which is obscuring many of the retinal vessels as they cross over the disc margin.

OTHER OPTIC NEUROPATHIES

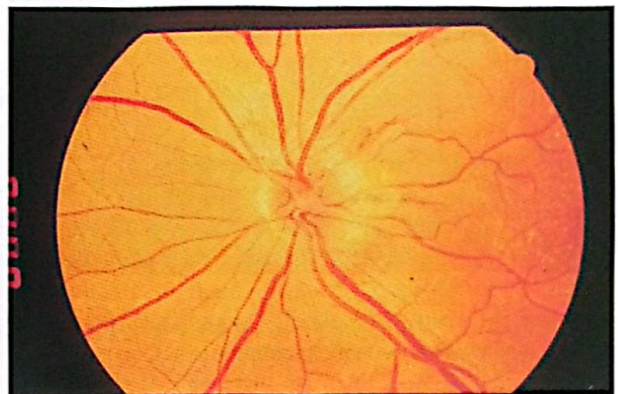


FIGURE 3.108 Micropapilla: "crowded disc" with impairment of papillary blood flow.



FIGURE 3.109 Micropapilla: crowded disc with marked retinal venostasis and papilledema.



FIGURE 3.110 Drusen of the disc which may impair papillary blood flow and cause visual field defects.

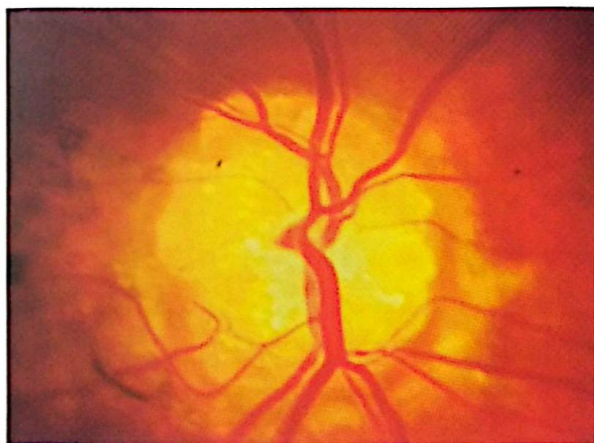


FIGURE 3.111 Severe optic nerve head drusen.

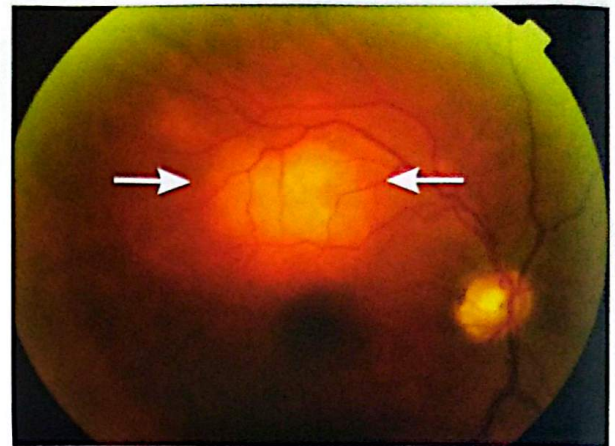


FIGURE 3.112 Right eye, color fundus photo showing choroidal metastasis of lung carcinoma. Note the creamy subretinal mass just superior to the fovea.

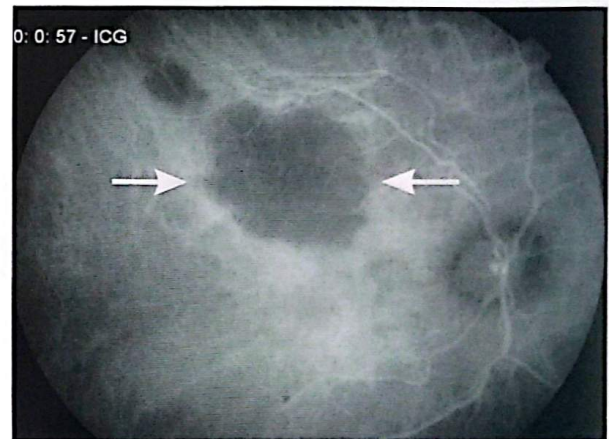


FIGURE 3.113 Same patient, 57" ICG angiography frame reveals hypofluorescence caused by the lesion, as seen clinically. This confirms the absence of an intrinsic choroidal vasculature and is consistent with a metastatic lesion, as opposed to a choroidal melanoma or choroidal hemangioma, which can exhibit an intrinsic vasculature sometimes well seen on ICG angiography.

Future Techniques

Despite the technical limitations of existing techniques, measurement of blood flow has been useful in diagnosing various diseases and ophthalmic pathologic conditions. As blood flow assessment improves—including differentiation of various vascular beds and assessment of other parameters, such as oxygen tension and metabolic measurements—the diagnostic efficacy of the measurements is sure to increase. Advances in the areas of hemodynamic, oxygen, and metabolic measurements are already underway.

In this section a new blood flow measurement technique and several oximetry measurement techniques are discussed. These measurement techniques are currently in use in academic clinical settings; however, they are not yet commercially available.

Neuroretinal Rim Blood Flow Evaluation

Accurate quantification of ocular blood flow is of increasing importance in studying glaucoma. Disturbances in blood supply to the optic nerve head are believed to be linked to disease progression.

As discussed in an earlier section, the confocal scanning laser Doppler flowmetry with the Heidelberg Retina Flowmeter (HRF; Heidelberg Engineering, Heidelberg, Germany) is a noninvasive technique that allows blood flow measurement in these specific areas. In most published studies, single HRF images containing both peripapillary retina and neuroretinal rim tissue have been acquired. The Doppler signal produced by the temporal peripapillary retina is much higher than in the rim, as measured by direct current (DC) values within the HRF image. (Direct current refers to the signal strength produced by the HRF's photodetector and is proportional to the intensity of reflected light.)

Previous studies showed that HRF measurements are affected by different DC levels; therefore, measurements in the neuroretinal rim area may provide inaccurate data because of improper sensitivity settings for the weaker rim signal. To accurately assess flow in the neuroretinal rim, the image of the neuroretinal rim area should be taken separately from the peripapillary

retinal area with an appropriately higher sensitivity setting and without producing pixels with excessively high DC values in other areas of the image.

A second important issue regards the region of interest, which must be accurately defined. Biomorphometric measurements of intrapapillary and parapapillary parameters have been performed for many years by planimetry and scanning laser tomography. Scanning laser tomography allows a three-dimensional quantification of optic nerve head tissue (Figure 4.1).

Bartz-Schmidt and coworkers developed a method to describe and quantify neuroretinal rim measurements and glaucomatous rim loss, using the Heidelberg Retina Tomograph (HRT) (Bartz-Schmidt, Weber, Heilmann, 1994) (Figure 4.2). Their aim was to normalize the papillary parameters to make individual measurements comparable with standardized ones, based on a collective of healthy individuals. In addition, a calculation of a rim-to-disc area ratio in 36 sectors of 10° (Figure 4.3) around the rim provided a generalized view of glaucomatous damage as cumulative distribution curves (Figure 4.4) similar to those previously described in perimetry. This important approach has also been criticized because of its loss of localized information. Clinicians are certainly interested not only in general information about the papillary morphology but also in localized changes over time, as in the occurrence of rim notching. In response to this need, the same group developed a technique of

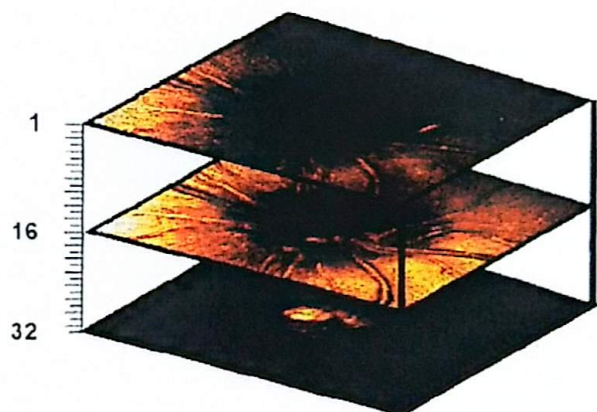


FIGURE 4.1

reprojecting these curves (Figure 4.5), within the topography of individual optic nerves, which ultimately allows for the localized and precise quantification of neuroretinal rim tissue damage over time (Figure 4.6). This approach has not been broadly implemented because of its technical complexity; it is only partly used in a program developed in Cologne, Germany, by the Laboratory of Biomorphometry and Retinal Perfusion Analysis (LBRPA) for its own clinical evaluation purposes and scientific approaches.

Researchers first described an approach of neuroretinal rim blood flow measurements with HRF using morphologic definitions by means of scanning laser tomography (Jonescu-Cuypers, Chung, Kagemann, 2001). This combination with morphologic quantification and quality assessment of papillar parameters has been pursued in order to better define the tissue border of interest, that is, the neuroretinal rim. An accurate definition of the area to be measured is particularly important to allow subsequent measurements of the same tissue over time. In this way, follow-up measurements of blood flow within the retinal tissue are more reliable. Figure 4.7 shows a scanning laser retinal tomographic image of the papilla of interest. In Figure 4.7, the contour line (green) defines the optic disc border as the outer edge of the neuroretinal rim.

The limit defining the inner edge of the neuroretinal rim can be achieved by using the HRT software to calculate stereometric parameters, depending on the definition of the standard reference plane (50 μm under the mean contour line height in the sector -4° to -10°).

Using the standard reference plane and depending on the drawn contour line, the optic disc can be represented as a colored image describing the optic disc topography as follows: red for the cup area and blue plus green for the neuroretinal rim (Figure 4.8). In this way, the inner edge of the rim can be defined as the transition between the blue-green and the red surface.

At this time, no existing digital technique can transpose HRT topography data to HRF flow maps; thus a method has been created to transfer the borders of the defined areas. Using a transparent overlay, the HRT-defined inner and outer edges of the rim, as well as the vessel contours, are drawn manually (Figure 4.9). Then the resulting template (Figure 4.10) is overlaid on the equivalent HRF images of the same subjects, adjusting the areas of interest (see Figures 4.11 to 4.13).

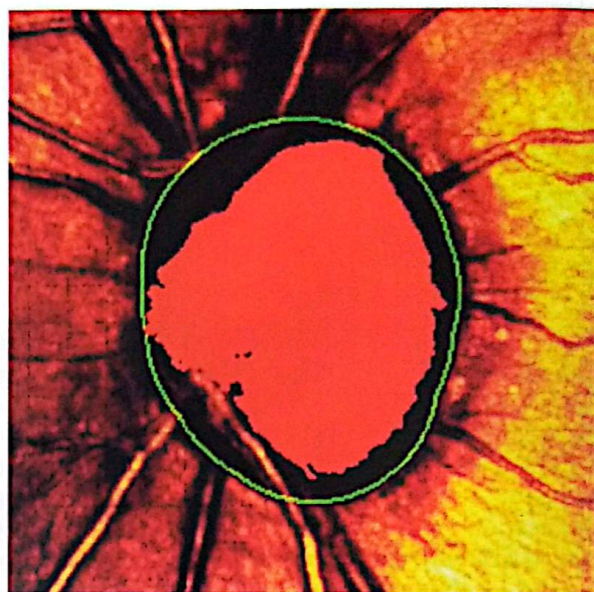


FIGURE 4.2 Figure reprinted from Bartz-Schmidt KU, Sengersdorf A, Esser P, et al. The cumulative normalised rim/disc area ratio curve. *Graefes Arch Clin Exp Ophthalmol* 1996; 234:227-31.

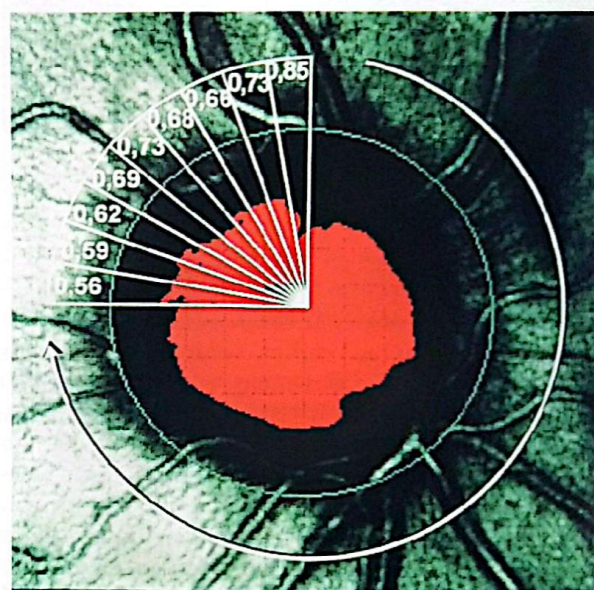


FIGURE 4.3 Figure reprinted from Bartz-Schmidt KU, Sengersdorf A, Esser P, et al. The cumulative normalised rim/disc area ratio curve. *Graefes Arch Clin Exp Ophthalmol* 1996; 234:227-31.

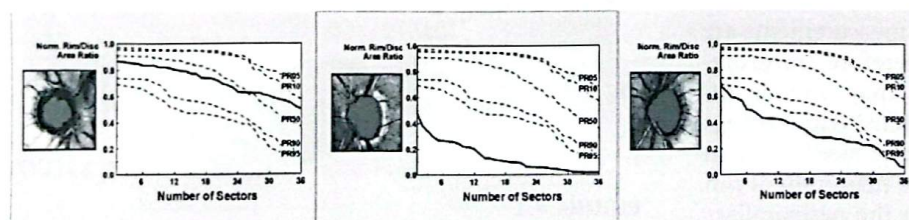


FIGURE 4.4 Figure reprinted from Bartz-Schmidt KU, Sengersdorf A, Esser P, et al. The cumulative normalised rim/disc area ratio curve. *Graefes Arch Clin Exp Ophthalmol* 1996; 234:227-31.

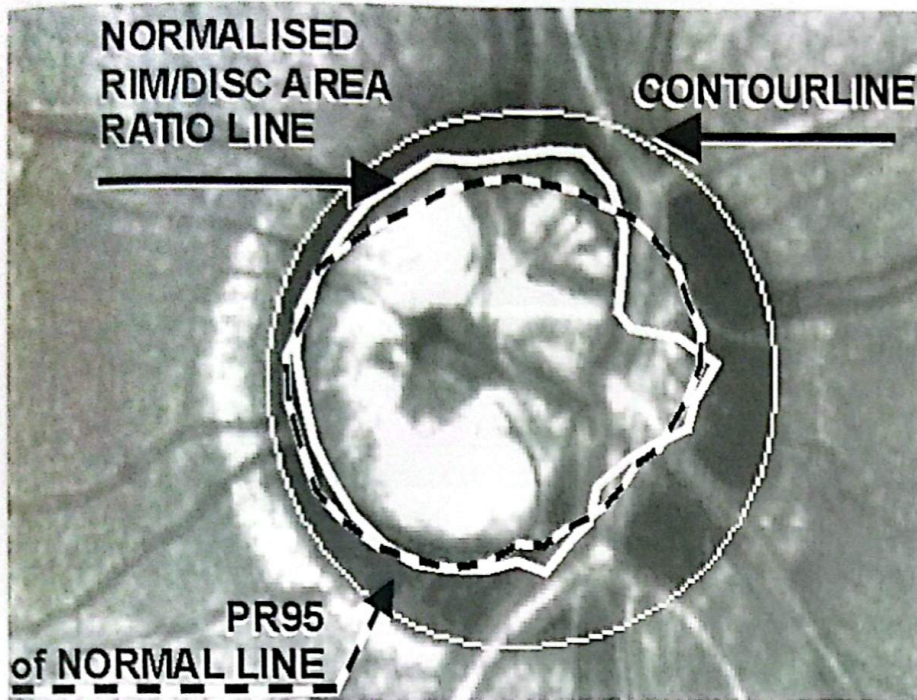


FIGURE 4.5 Figure reprinted from Bartz-Schmidt KU, Sengersdorf A, Esser P, et al. The cumulative normalised rim/disc area ratio curve. Graefes Arch Clin Exp Ophthalmol 1996; 234:227-31.

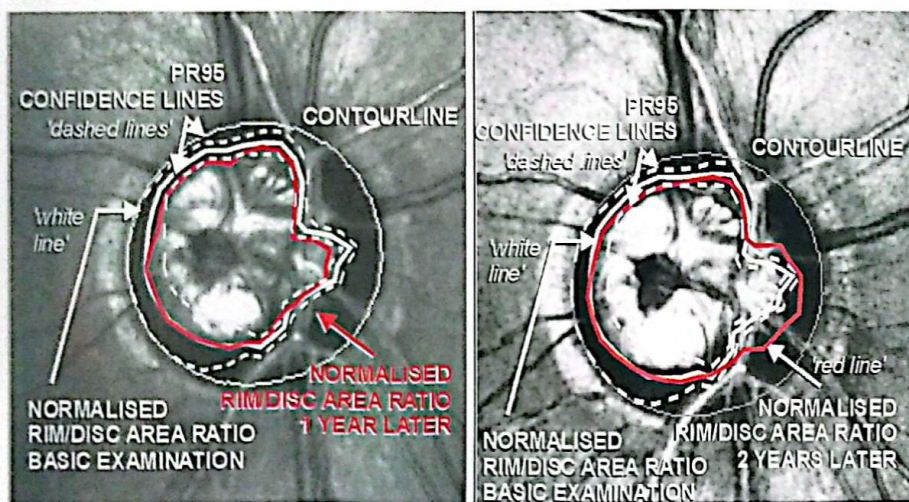


FIGURE 4.6 Figure reprinted from Bartz-Schmidt KU, Sengersdorf A, Esser P, et al. The cumulative normalised rim/disc area ratio curve. Graefes Arch Clin Exp Ophthalmol 1996; 234:227-31.

Images of identical tissue locations (*shaded area*, in this example) of the neuroretinal rim, identified by vascular landmarks and the contour line (transferred from HRT images), are selected to quantify the microcirculation of the neuroretinal rim.

HRF images are acquired using the standard $10^\circ \times 2.5^\circ$ measurement field, with each two-dimensional image consisting of 256 pixels $\times$ 64 lines. The images of each examined papilla must be obtained first, following a conventional setting, which has the optic nerve head in the center of the image with photodetector sensitivity optimized for the strong signal from the temporal peripapillary retina. Flanagan et al. described a method to accurately

focus on the peripapillary retina, allowing the correct setting for HRF measurements that use only 400 μm of depth.

Because of its weak signal, the conventional acquisition method produces an image with a dark rim area (Figure 4.11). The setting then must be altered with signal capturing optimized on the rim by increasing the sensitivity. (Increasing sensitivity is a procedure to provide proper signals from the dark rim area; Figure 4.12.) Once the level of increased sensitivity is reached, the temporal rim margin must be moved tangent to the lateral image border to avoid the overpowering signal from the temporal peripapillary retina, thereby removing overilluminated areas (Figure 4.13).

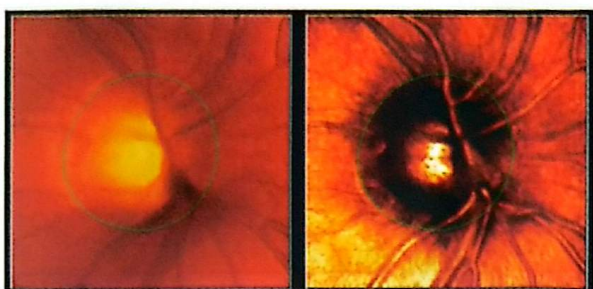


FIGURE 4.7 Image courtesy of Christian P Jonescu-Cuyppers, Hak S Chung, Larry Kagemann, Yoko Ishii, Drora Zarfati, Alon Harris. *Br J Ophthalmol* 2001;85:304-309.

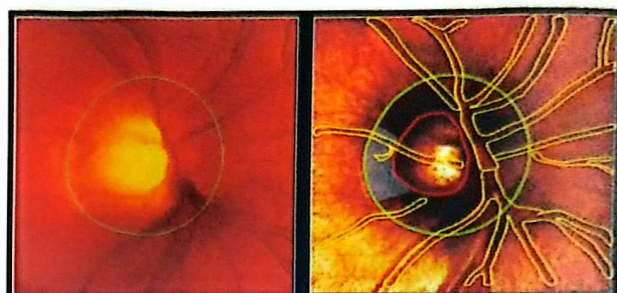


FIGURE 4.9 Image courtesy of Christian P Jonescu-Cuyppers, Hak S Chung, Larry Kagemann, Yoko Ishii, Drora Zarfati, Alon Harris. *Br J Ophthalmol* 2001;85:304-309.

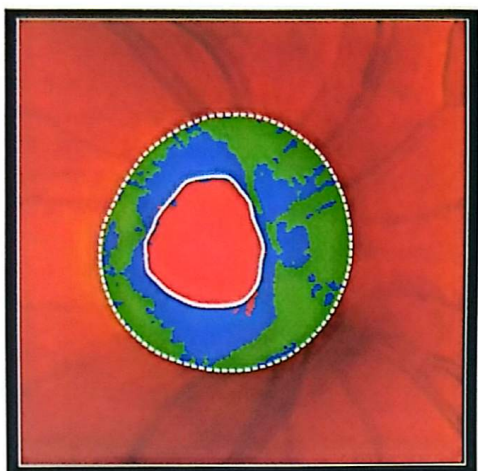


FIGURE 4.8 Image courtesy of Christian P Jonescu-Cuyppers, Hak S Chung, Larry Kagemann, Yoko Ishii, Drora Zarfati, Alon Harris. *Br J Ophthalmol* 2001;85:304-309.

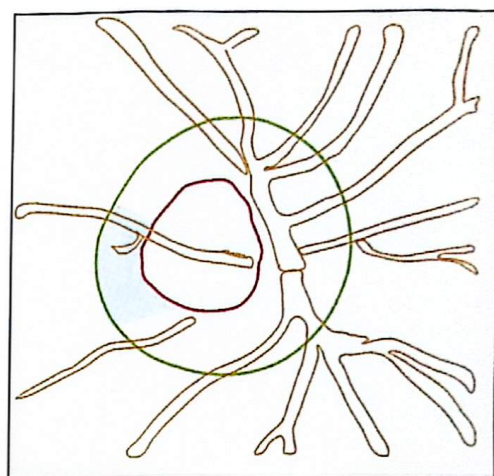


FIGURE 4.10 Image courtesy of Christian P Jonescu-Cuyppers, Hak S Chung, Larry Kagemann, Yoko Ishii, Drora Zarfati, Alon Harris. *Br J Ophthalmol* 2001;85:304-309.

This method provides an accurate and reproducible flow measurement of the neuroretinal rim area through proper sensitivity settings for the weak rim signal, alignment, and removal of the strong temporal signal from the image. For further analysis, it is also important to use the correct technique of pixel evaluation, specifically the pointwise analysis.

As mentioned earlier, no technique for automatic combined measurements is available yet, but the LBRPA is developing corresponding technical approaches that will be available in the near future.

Laser Speckle Flowmetry

Illumination of the fundus with a coherent light source produces a number of interference phenomena. The Nerve Fiber Layer Analyzer or GDx (Laser Diagnostic Technologies, Inc., San Diego, CA), for example, uses a coherent light source combined with birefringence of the fundus to measure the thickness of the nerve fiber layer. Interferometry, as discussed previously, uses the interference pattern that is created by light reflected from the



FIGURE 4.11 Image courtesy of Christian P Jonescu-Cuyppers, Hak S Chung, Larry Kagemann, Yoko Ishii, Drora Zarfati, Alon Harris. *Br J Ophthalmol* 2001;85:304-309.

fundus and anterior surface of the cornea to measure the amplitude of fundus pulsation within the cardiac cycle.

A laser speckle flowmeter has been developed to quantify the rate of variation in the speckle pattern as a surrogate for the measurement of volumetric retinal blood flow. The speckle phenomenon is observed as a speckled pattern of light, which is scattered from the fundus when illuminated by a coherent source. The pattern varies rapidly within the cardiac cycle. The rate of pattern variation depends on the magnitude of retinal blood flow. Variations in the speckle pattern are quantified point by point throughout the fundus, and a flow map is created. Earlier photographic methods



FIGURE 4.12 Image courtesy of Christian P Jonescu-Cuyper, Hak S Chung, Larry Kagemann, Yoko Ishii, Drora Zarfati, Alon Harris. *Br J Ophthalmol* 2001;85:304-309.



FIGURE 4.13 Image courtesy of Christian P Jonescu-Cuyper, Hak S Chung, Larry Kagemann, Yoko Ishii, Drora Zarfati, Alon Harris. *Br J Ophthalmol* 2001;85:304-309.

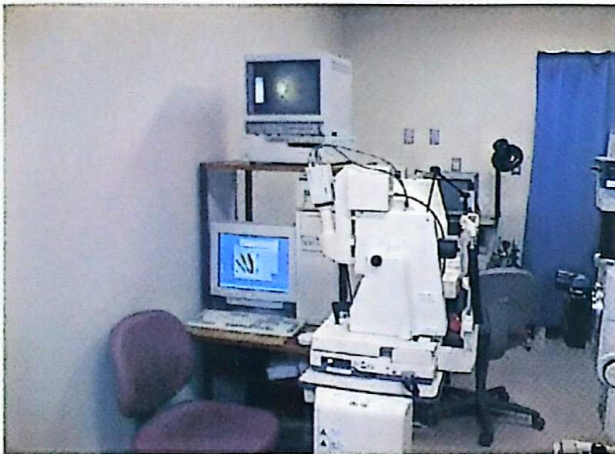


FIGURE 4.14 Image courtesy of Dr. Yasuhiro Tamaki.

using the speckle phenomenon could display the distribution of velocity in the retina; however, despite the advantage of producing a distributive description of retinal blood velocities, it only allowed a semiquantitative estimation of retinal microcirculation and could not follow time course changes.

Recently, researchers have described an improved apparatus for noncontact two-dimensional measurement of the microcirculation in the optic nerve head (Figure 4.14) (Tamaki, Araie, Kawamoto, 1994). Their apparatus consists of a Topcon TRC-WT3 fundus camera, equipped with an 808-nm diode laser (Figure 4.15). Normalized blur is calculated for each pixel within a 0.62×0.62 mm area of the retina. Normalized blur is equal to the average reflected intensity divided by the absolute difference between average intensity and a 98-point floating average (Figure 4.16). A normalized blur map has been created from speckle originating within the optic nerve head tissue in Figure 4.17. Note the high signal obtained from blur within the vessel compared with the surrounding tissue.

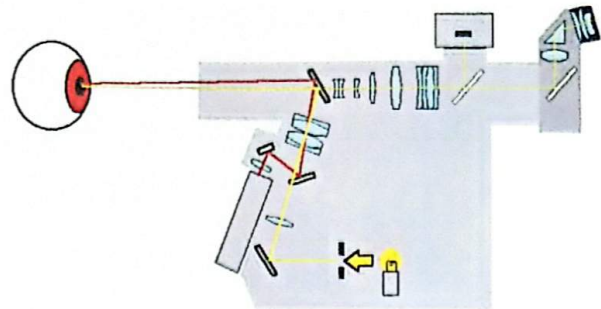


FIGURE 4.15 Image courtesy of Dr. Yasuhiro Tamaki.

Normalized Blur

Mean

$$\frac{1}{98} \sum_{i=1}^{98} |\text{Mean} - \text{Intensity } i|$$

FIGURE 4.16

Laser speckle flowmetry is a noninvasive technique that can measure a blood velocity parameter, albeit in arbitrary units (Figure 4.18). Furthermore, the technique has been proven to have reproducible measurements. The two greatest disadvantages of the technique are that (1) the technology is not commercially available and (2) the meaning of the raw normalized blur measurement is not clearly understood (Figure 4.19).

The technique is appropriate for the measurement of change over time if the optics are not significantly altered. The effect of a progressive cataract on laser speckle measurements is unknown.

Digital Spectral Retinal Oximetry

Noninvasive oxygen measurement is based on optical methods that detect the ratio of oxygenated (red) to deoxygenated (blue) hemoglobin in red blood cells. As evidenced by their different colors, oxygenated and deoxygenated hemoglobin possess different optical characteristics. Measurement involves passing two wavelengths of light through (or reflecting from them) the tissue of interest. The ratio between the resulting light intensities represents oxygen tension.

The optical characteristics of blood are objectively quantified. The definitive work describing the optical characteristics of blood was published in 1970 in a book by Van Assendelft called *Spectrophotometry of Hemoglobin Derivatives*. The work measures the extinction

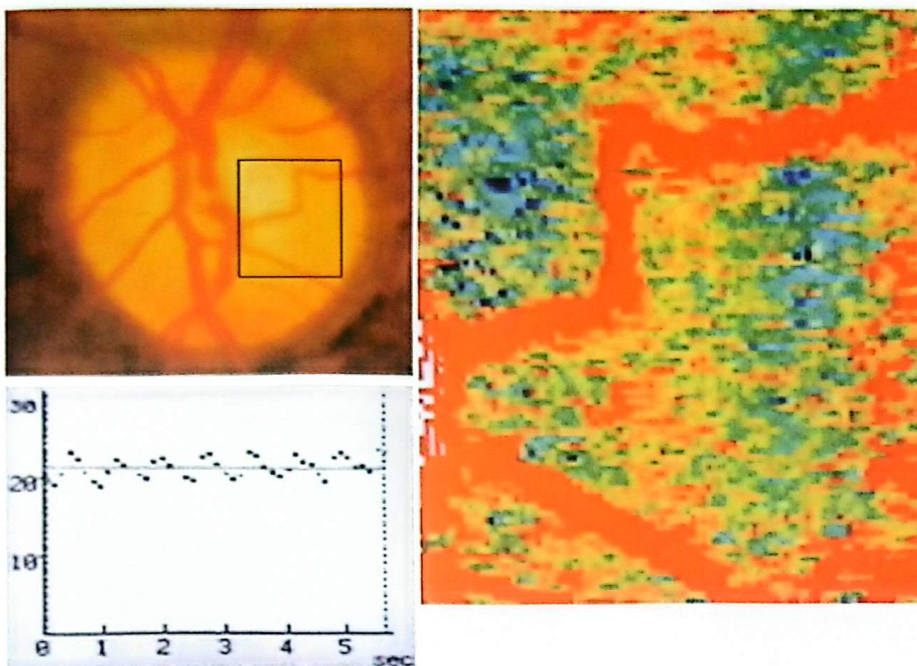


FIGURE 4.17 Image courtesy of Dr. Yasuhiro Tamaki.

Pros
- Non-invasive - Index of Tissue Velocity - Validated: - In vitro ground glass speckle phantom - In-vivo with microspheres - In-vivo with IOP Elevation

FIGURE 4.18

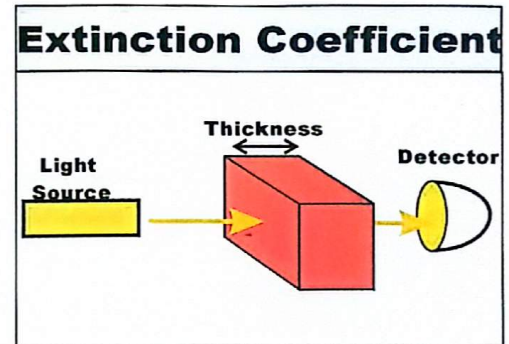


FIGURE 4.20

Cons
- Tissue blood velocity index - Not flow - Not an absolute measure

FIGURE 4.19

Extinction Coefficient
$\text{Light out} = \text{Light in} \times e^{-\mu t}$ t = Thickness μ = Extinction Coefficient

FIGURE 4.21

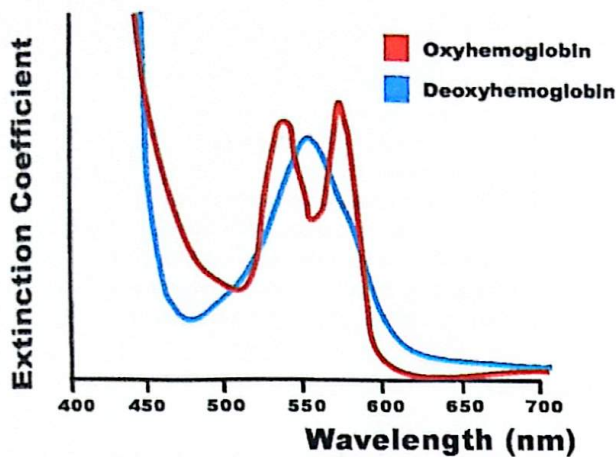


FIGURE 4.22

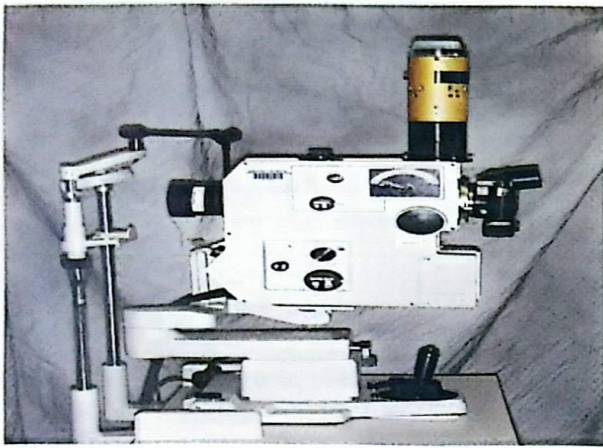


FIGURE 4.23

coefficient, which is the success or failure of light of every frequency to pass through blood (Figure 4.20). Figure 4.21 provides the equation relating the intensity of light going into the blood column, the light leaving the blood, the thickness (t), and the extinction coefficient (μ). The penetration of light also depends on the frequency of the light and whether the blood is oxygenated or deoxygenated. Specific extinction coefficients for both oxygenated (HbO_2) and deoxygenated (Hb) hemoglobin can be graphed as a function of light frequency (Figure 4.22). Wavelengths of interest are located in the spectrum from 450 to 650 nm. The graphs show that light at 558 nm, for example, passes more easily through oxygenated blood since the HbO_2 graph is lower at that wavelength. There are wavelengths such as 586 nm where HbO_2 and Hb have identical effects on light. These are defined as isosbestic wavelengths.

To measure the red/blue blood ratio, two wavelengths of light are passed through (or bounced off) the tissue of interest. One color of light is at an isosbestic wavelength, and the other is at a wavelength such as 558 nm where there is a large difference in the absorption of

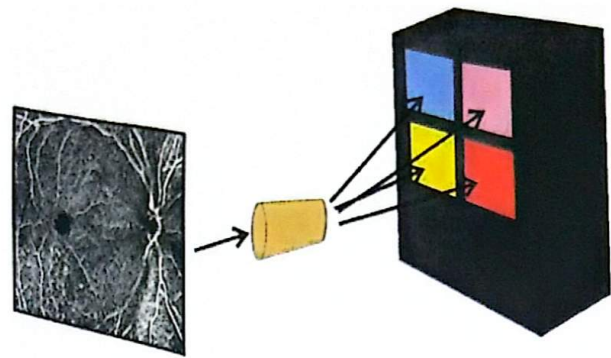


FIGURE 4.24

light between red and blue blood (see Figure 4.22). Reflected light is measured. The log of the ratio between the original light intensity and the reflected light intensity is defined as the optical density (OD). To convert an 8-bit grayscale image to an OD image, for example, the new value of each pixel is equal to $\log(255/\text{pixel})$.

It may seem curious to discuss a grayscale image when four "colors" are being quantified. The Glaucoma Research and Diagnostic Center has developed a retinal oximeter that measures multiple wavelengths of light from a fundus image (Figure 4.23). Each "color" of interest is actually a 5-nm-wide band of colors surrounding a carefully chosen wavelength of interest. The gold-colored addition at the top of the camera is the heart of the system. A custom-made optics package divides a single image into four images, and filters out wavelengths of interest (Optical Insights; LLC, Santa Fe; Figure 4.24). The intensity of reflected light at each of these four wavelengths is quantified by a single charge-coupled-device photodetector (Figure 4.25). The intensity of each of the four colors is assigned a value in between 0 (black, or no intensity) and 255 (equal to the intensity of the incident light) and displayed as a grayscale image (see Figure 4.25).

The ratio between two wavelengths is used to create an optical density ratio (ODR) image or map. The ODR is sensitive to changes in oxygen saturation in blood within retinal vessels. An ODR map is shown in Figure 4.26. In this image, darker areas contain higher concentrations of oxygenated hemoglobin. Experiments with three and four wavelengths are currently underway, in an effort to increase the sensitivity of the system.

Previously, blood flow measurements have acted as surrogates for direct measurements of metabolism, providing an indication of oxygen delivery to the retina. This system has the advantages of being noninvasive and performing measurements of oxygen saturation within blood. If measurements of oxygenated hemoglobin saturation within arterial and venous blood are combined with retinal blood flow measurements, volumetric oxygen delivery to retinal tissue will be possible (Figure 4.27). The greatest disadvantage of the system is

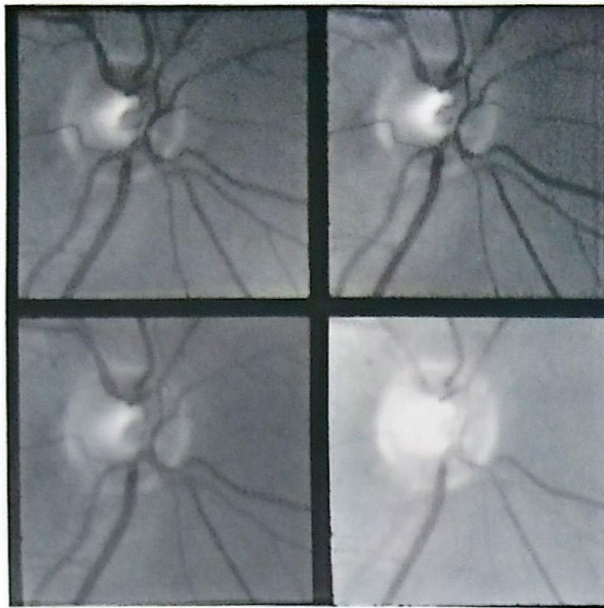


FIGURE 4.25

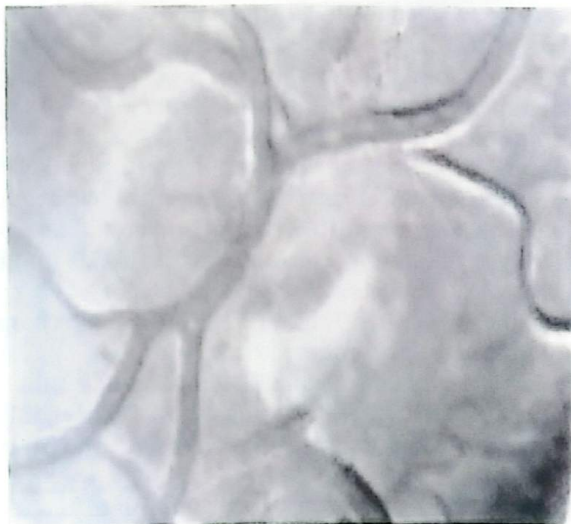


FIGURE 4.26

that the measurement depends on light intensity. Intensity is subject to many sources of noise within the human eye, such as cataract, floaters, and so on. These noise sources vary among eyes, necessitating customized system calibration for each patient (Figure 4.28).

Ischemia is a known pathophysiologic factor in a number of eye diseases, such as diabetic retinopathy, anterior ischemic optic neuropathy, and various vein and artery occlusion diseases. In diseases such as age-related macular degeneration and glaucoma (the two leading causes of blindness in the United States), epidemiology studies have found vascular risk factors associated with the disease, but the role of ischemia is

Pros

- Non-invasive
- Measurement of oxygen saturation in blood
- Combination of arterial and venous measurements allows calculation of oxygen extraction
- Combined with blood flow, allows Calculation of oxygen delivery

FIGURE 4.27

Cons

- Requires an accurate light intensity measurement
- Difficult to calibrate
- Best four image oxymetry calculation not yet known

FIGURE 4.28

unknown. This is because, previously, no noninvasive technology was capable of fundus oximetry.

The application of oximetry measurements to study basic ophthalmic disease processes, as well as the pharmaceutical effects of existing topical medications on retinal oxygen tension, is of immense interest to government funding agencies and pharmaceutical companies alike.

Magnetic Resonance Oximetry

Magnetic resonance oximetry measurements are based on the principle that oxygen is a paramagnetic compound and directly influences the spin-lattice relaxation rate ($1/T_1$) (Figure 4.29). The T_1 relaxation time is a function of many factors besides local oxygen tension. To eliminate other factors, such as flow, that can affect the observed T_1 , measurements are limited to the posterior vitreous near the retina. Oxygenation of the posterior vitreous near the retina is used as a measure of inner retinal oxygenation.

To highlight the potential application of magnetic resonance imaging (MRI) retinal ΔPO_2 measurement to study a wide range of experimental models of retinopathy, representative high-resolution T_1 -weighted cross sections of eyes in vivo are presented in Figure 4.30.

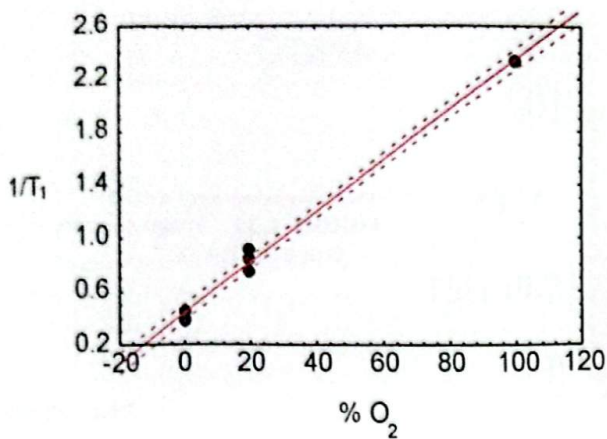


FIGURE 4.29 Image courtesy of Dr. Bruce Berkowitz.

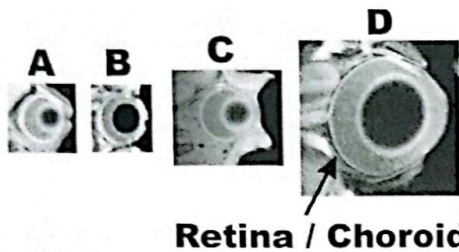


FIGURE 4.30 Image courtesy of Dr. Bruce Berkowitz. Figure reprinted from Berkowitz BA, Kowluru RA, Frank RN, Kern TS, Hohman TC, Prakash M. Subnormal retinal oxygenation response precedes diabetic-like retinopathy. *Invest Ophthalmol Vis Sci*. 1999;40:2100-2105.

Image A is a newborn mouse (P17, 3.5 g, eye diameter 2.5 mm, $50 \mu\text{m}^2$ in-plane resolution, 1-mm slice thickness). Image B was obtained from an adult mouse (24 g, eye diameter 3 mm). Image C is the eye of a newborn rat (P14, 24 g, diameter 3 mm), and image D is the eye of an adult rat (300 g, diameter 6 mm). These images took either 2 (Figure 4.30 A-C) or 8 (Figure 4.30 D) minutes to collect and are presented to scale. Acquisition parameters are presented elsewhere. Note the retina-choroid complex (seen as a white line in the posterior region of the eye; arrow in Figure 4.30) as it extends from superior to inferior ora serrata.

ΔPo_2 : Simply obtaining an image of the eye during room air breathing alone cannot be used to measure retinal oxygenation from an MRI (Figure 4.31). Many factors affect the baseline preretinal vitreous water signal and its relaxation properties. Instead, the increase in partial oxygen pressure in the vitreous over the room air value (ΔPo_2) during a hyperoxic inhalation challenge is detected as an increase in the signal intensity on a T_1 -weighted image (Figure 4.32). To quantify the change in oxygen tension, the baseline and carbogen images are subtracted and the resulting changes are converted to ΔPo_2 on a pixel-by-pixel basis (Figure 4.33). Carbogen gas (95% O_2 /5% CO_2) is used

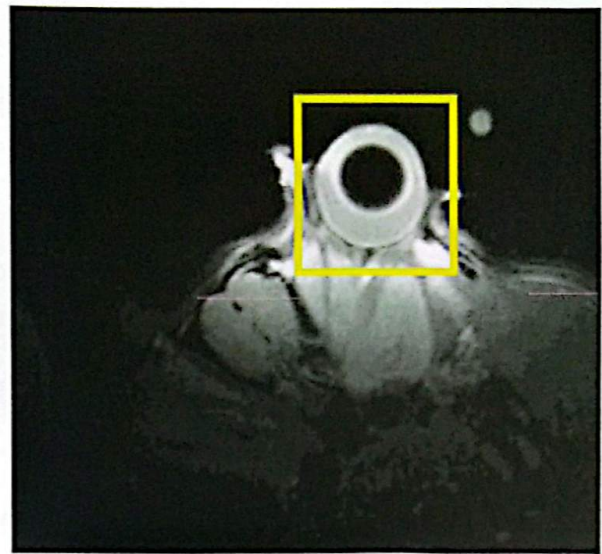


FIGURE 4.31 Image courtesy of Dr. Bruce Berkowitz.

Room Air Carbogen

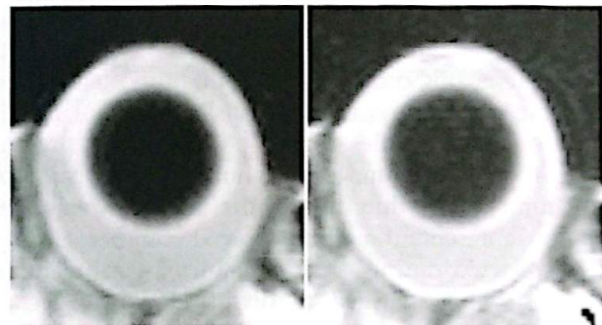


FIGURE 4.32 Image courtesy of Dr. Bruce Berkowitz.

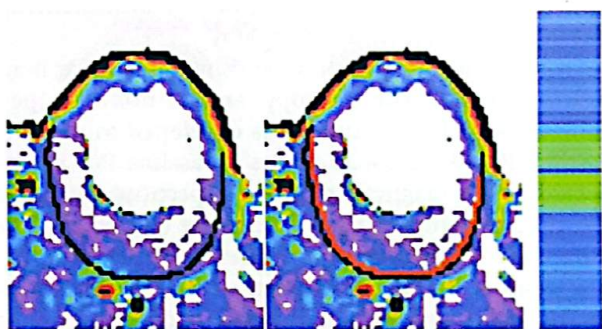


FIGURE 4.33 Image courtesy of Dr. Bruce Berkowitz.

clinically to prevent the retinal vasoconstriction produced during 100% oxygen breathing and is thought to produce a larger oxygenation response than pure oxygen inhalation. Research has confirmed that carbogen breathing does result in a roughly 50% improvement in retinal oxygenation compared with 100% oxygen

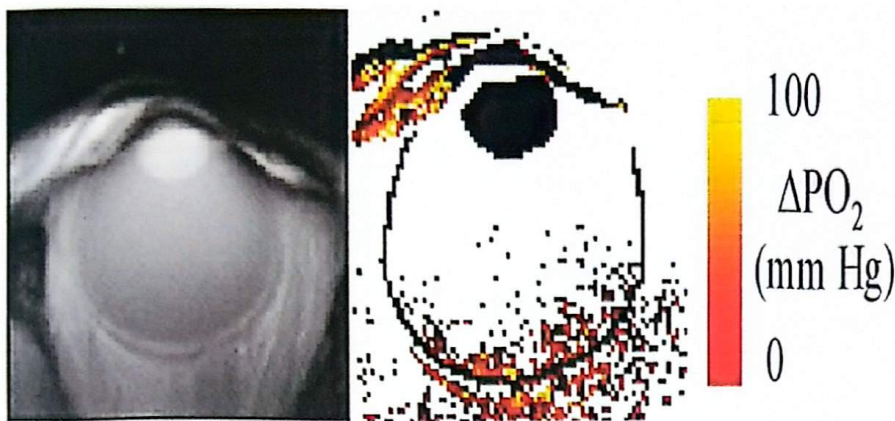


FIGURE 4.34 Image courtesy of Dr. Bruce Berkowitz.

breathing in the Sprague-Dawley rat (Berkowitz, 1996). Thus, subtle differences in the ability of the retina to oxygenate are more readily determined during carbogen breathing than during 100% oxygen breathing. The MRI measured Po_2 is similar to those that derived from oxygen electrode measurements during a hyperoxic inhalation challenge in normal rats.

The major advantages and disadvantage of this technique are listed in Figures 4.35 through 4.37. The fMRI approach is not only accurate but, importantly, the ΔPo_2 measurement is readily translatable from preclinical to clinical studies. Figure 4.34 shows a representative T_1 weighted image of a human eye (pixel size 0.39 mm^2). The white line in the posterior region of the eye represents the retina/choroid complex. Images were collected during room air and oxygen breathing (10 min) and analyzed as discussed above (Figure 4.33). Note that brighter colors indicate greater oxygenation responses. These images demonstrate proof-of-concept and may help motivate future clinical evaluation of MRI retinal oxygenation measurements and its association with retinopathy.

Po_2 : An additional technique using ^{19}F nuclear magnetic resonance spectroscopy and a nontoxic perfluorocarbon (PFC) droplet was developed to measure baseline Po_2 . Figure 4.38 shows a baseline Po_2 image, created by ^{19}F magnetic resonance spectroscopy, and a PFC droplet, which is used to measure oxygen tension. The preretinal vitreous Po_2 is measured from the $(T_1)^{-1}$ of a small ($0.3 \mu\text{l}$) PFC droplet, such as perfluoro-15-crown-5-ether, injected onto the surface of the retina several days before the examination. This procedure allows the eye to recover from the surgery. However, if necessary, the droplet can be injected into the preretinal vitreous on the day of the experiment. Note that patients following vitrectomy with a PFC vitreous substitute may have some residual droplets that can also be studied. Similar to the previous method, $1/T_1$ is a function of oxygen tension; however, in this technique, the T_1 must be corrected for the PFC

Pros
- Accurate - Non-invasive - Wide applicability (rodent to human) - Does not require a perfluorocarbon droplet

FIGURE 4.35

Pros
- Not affected by media opacities - Simultaneously measures the retinal oxygenation response from superior to inferior ora serrata

FIGURE 4.36

temperature. To accurately estimate the preretinal vitreous Po_2 , temperature from the droplet is measured independently using ^{19}F NMR spectroscopy as previously described. High-resolution MRI is used to determine the droplet diameter and position in the vitreous (regardless of the presence of cataracts). Figure 4.38 is a representative MRI ($90 \mu\text{m}$ in plane

Cons
- Does not measure baseline PO_2

FIGURE 4.37

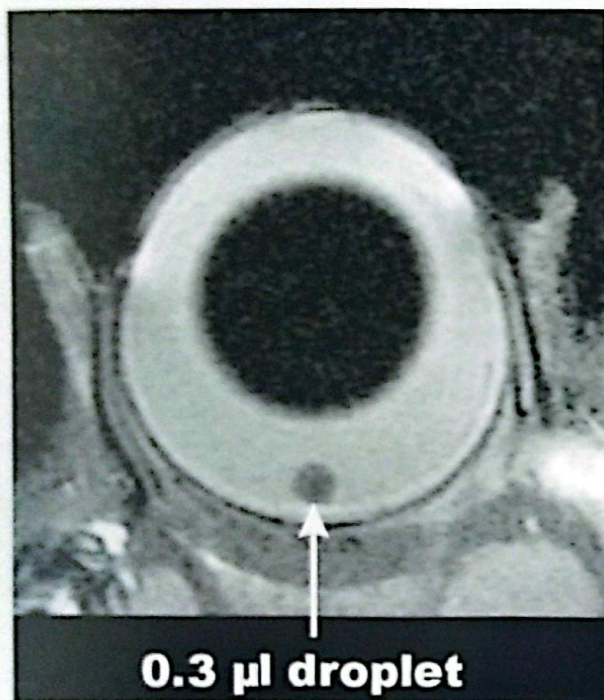


FIGURE 4.38 Image courtesy of Dr. Bruce Berkowitz. Figure reprinted from Berkowitz BA, Kowluru RA, Frank RN, Kern TS, Hohman TC, Prakash M. Subnormal retinal oxygenation response precedes diabetic-like retinopathy. *Invest Ophthalmol Vis Sci.* 1999;40:2100-2105.

resolution, 1-mm slice thickness) of a 0.3- μ l PFC droplet on the retina of a control adult rat eye. The PFC droplet does not contain any protons and shows up as a "black hole" on a proton image. As previously demonstrated, the ^{19}F measurement of PO_2 is accurate when compared with oxygen electrode measures. This technique is widely applicable in preclinical research (Figure 4.40). However, data acquisition requires a drop of PFC, and the spatial resolution is limited (Figure 4.41). In addition, clinical application is ethically limited to a relatively small patient population (those that have residual PFC droplets after surgery).

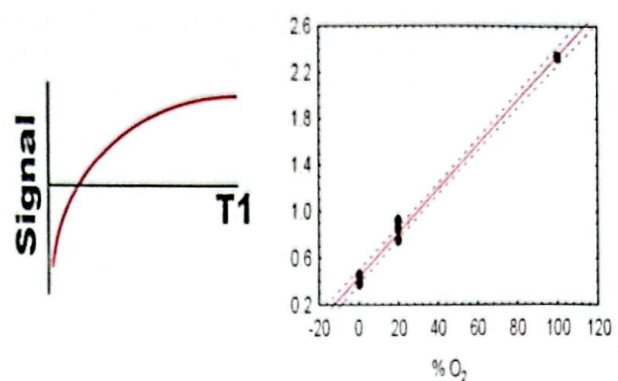


FIGURE 4.39 Image courtesy of Dr. Bruce Berkowitz.

Pros
- Accurate - Non-destructive - Wide applicability (rodent to Human) - Not affected by media opacities

FIGURE 4.40

Cons
- Requires a perfluorocarbon droplet - Needs temperature correction - Limited spatial resolution

FIGURE 4.41

Conclusion

Although preliminary data is available, thorough validation of each of these techniques is necessary before their data merit acceptance. The more specific the measurement, the more difficult the validation becomes. For example, assessing the true accuracy of the HRF, as discussed in Section 2, would require a capillary model containing human blood, flowing through 10- to 15- μ m diameter tubes surrounded by the axons of the nerve fiber layer. The HRF is affected by the optical

characteristics to the tissue being measured; therefore, known flow rates would be required in a controlled environment identical to that of the fundus. Despite the fact that technology has advanced to the point of being able to create and construct a scanning laser Doppler flowmeter, we still cannot construct a 10- μ m diameter capillary tube in which blood will not clot. The ideal flow phantom (a device mimicking blood flow of a known quantity with physical characteristics identical to human tissue) for the HRF cannot yet be built. Similar issues exist in the validation of the various oximetry techniques. Autofluorescence of retinal pigments, the various absorption spectra of pigments in the fundus, and variable yellowing of the lens with age all act to create sources of noise and error that must be taken into account before precise validation and calibration of spectral oximetry can be completed.

Validating our measurements is just the first step. Only then may clinical scientists begin taking these measurements in the highly variable environment of the healthy eye. From there, the study of injury, disease,

medication, surgical procedures, and growth may progress. Ultimately, longitudinal data may provide the most meaningful insights into the complex interplay of hemodynamics, metabolism, and ocular health. However, little or no longitudinal data has yet to be obtained from even the oldest of the technologies discussed in Section 2. Longitudinal oximetry measurements are most likely years away.

Acknowledgements for images Section 4:

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References

- Abum NS, Sergott RC. Orbital colour Doppler imaging. *Eye*. 1993;7:639-647.
- Adler FH. 1895 *Adler's Physiology of the Eye: Clinical Application*, edited by William M. Hart, Jr. 9th ed. St. Louis, Mo: Mosby; c1992.
- Age-Related Eye Disease Study Research Group. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. *Arch Ophthalmol* 2001 Oct;119(10):1417-1436.
- Alm A. Ocular circulation. In: Hart WM, ed. *Adler's Physiology of the Eye*. 9th ed. St. Louis, Mo: Mosby; 1992:198.
- Anderson DR. Introductory comments on blood flow autoregulation in the optic nerve head and vascular risk factors in glaucoma. *Surv Ophthalmol*. 1999;43(suppl 1):S5-9. Review.
- Anderson DR. Ultrastructure of human and monkey lamina cribrosa and optic nerve head. *Arch Ophthalmol*. 1969; 82:800.
- Anderson DR. Vascular supply to the optic nerve of primates. *Am J Ophthalmol*. 1970;70:341.
- Anderson DR, Braverman S. Reevaluation of the optic disc vasculature. *Am J Ophthalmol*. 1976;82:165.
- Anderson DR, Hoyt WF. Ultrastructure of the intraorbital portion of human and monkey optic nerve. *Arch Ophthalmol*. 1969;82:506.
- Anderson T, Meredith I, Ganz P, Selwyn A, Yeung A. Nitric oxide and nitrovasodilators: similarities, differences and potential interactions. *J Am Coll Cardiol*. 1994;24:555-566.
- Araki M. Anatomical study of the vascularization of optic nerve. *Acta Soc Ophthalmol Jpn*. 1975;79:101.
- Arend A, Harris A, Martin BJ. Perifoveal capillary microcirculation: comparison of blue light simulation and scanning laser technique. *Graefes Arch Clin Exp Ophthalmol*. 1995;233:244-249.
- Arend O, Remky A, Evans D, Stuber R, Harris A. Contrast sensitivity loss is coupled with capillary dropout in patients with diabetes. *Invest Ophthalmol Vis Sci*. 1997;38:1819-1824.
- Arend O, Remky A, Harris A, Bertram B, Reim M, Wolf S. Macular microcirculation in cystoid maculopathy of diabetic patients [see comments]. *Br J Ophthalmol*. 1995;79:628-632.
- Arend O, Remky A, Solbach U. Digital fluorescein angiography in follow-up of the clinical course in therapy of patients with central vein occlusion and cystoid macular edema. *Klin Monatsbl Augenheilkd*. 1996;209:163-170.
- Arend O, Wolf S. Segmentation of fluorescence in the retinal microcirculation—Is it a valid indicator of blood cell flow? [reply]. *Br J Ophthalmol*. 1992;76:510-511.
- Arend O, Wolf S, Harris A, Reim M. The relationship of macular microcirculation to visual acuity in diabetic patients. *Arch Ophthalmol*. 1995;113:610-614.
- Arend O, Wolf S, Jung E, et al. Retinal microcirculation in patients with diabetes mellitus: dynamic and morphological analysis of perifoveal capillary network. *Br J Ophthalmol*. 1991;75:514-518.
- Arend O, Wolf S, Remky A, et al. Perifoveal microcirculation with non-insulin dependent diabetes mellitus. *Graefes Arch Clin Exp Ophthalmol*. 1994;232:225-231.
- Arnold JV, Gates HW, Taylor KM. Possible errors in the measurement of retinal lesions. *Invest Ophthalmol Vis Sci*. 1993;34:2576-2580.
- Augsten R, Konigsdorffer E, Schweitzer D, Strobel J. Multisubstance analysis of reflection spectra before and after laser photocoagulation for proliferative diabetic retinopathy. *Eur J Ophthalmol*. 1997;7:317-321.
- Bartz-Schmidt KU, Jonescu-Cuypers CP, Thumann G, et al. Influence of the contourline on the cup area using the Heidelberg Retina Tomograph [Zum einfluss der konturlinie auf die exkavationsflache beim Heidelberg retina tomograph]. *Klin Monatsbl Augenheilkd*. 1996;209:292-297.
- Bartz-Schmidt KU, Jonescu-Cuypers CP, Thumann G, et al. The normalised rim/disc area ratio line. *Int Ophthalmol*. 1995;19:331-335.
- Bartz-Schmidt KU, Sengersdorf A, Esser P, et al. The cumulative normalised rim/disc area ratio curve. *Graefes Arch Clin Exp Ophthalmol*. 1996;234:227-231.
- Bartz-Schmidt KU, Sundtgen M, Widder RA, et al. Limits of two-dimensional planimetry in the follow-up of glaucomatous optic discs. *Graefes Arch Clin Exp Ophthalmol*. 1995; 233:284-290.
- Bartz-Schmidt KU, Weber J, Heimann K. Validity of two-dimensional data obtained with the Heidelberg Retina Tomograph as verified by direct measurements in normal optic nerve heads. *Ger J Ophthalmol*. 1994;3:400-405.
- Baxter GM, Williamson TH, McKillop G, Dutton GN. Color Doppler ultrasound of orbital and optic nerve blood flow: effects of posture and timolol 0.5%. *Invest Ophthalmol Vis Sci*. 1992;33:604-610.
- Baxter GM, Williamson TH. Color Doppler flow imaging in central retinal vein occlusion: a new diagnostic technique? *Radiology*. 1993;187:847-850.
- Baxter GM, Williamson TH. Color Doppler imaging of the eye: normal ranges, reproducibility, and observer variation. *J Ultrasound Med*. 1995;14:91-96.
- Beach JM, Schwenzer KJ, Srinivas S, Kim D, Tiedeman JS. Oximetry of retinal vessels by dual-wavelength imaging: calibration and influence of pigmentation. *J Appl Physiol*. 1999;86:748-758.
- Bebie H, Flammer J, Bebie T. The cumulative defect curve: separation of local and diffuse components of visual field damage. *Graefes Arch Clin Exp Ophthalmol* 1999; 227:9-12.

- Behrendt T. Scanning densitometer for photographic fundus measurements. *Am J Ophthalmol.* 1966;62:689-693.
- Bennet AG, Rudnicka AR, Edgar DF. Improvements on Littmann's method of determining the size of retinal features by fundus photography. *Graefes Arch Clin Exp Ophthalmol.* 1994;32:361-367.
- Ben-Nun J, Constable JJ. Segmentation of fluorescence in the retinal microcirculation—Is it a valid indicator of blood cell flow? [letter]. *Br J Ophthalmol.* 1992;76:510.
- Berges O. Colour Doppler flow imaging of the orbital veins. *Acta Ophthalmol Suppl.* 204:55-58, 1992.
- Berkowitz BA. Adult and newborn rat inner retinal oxygenation during carbogen and 100% oxygen breathing. Comparison using magnetic resonance imaging delta P_{O_2} mapping. *Invest Ophthalmol Vis Sci.* 1996;37:2089-2098.
- Berkowitz BA, Kowluru RA, Frank RN, Kern TS, Hohman TC, Prakash M. Subnormal retinal oxygenation response precedes diabetic-like retinopathy. *Invest Ophthalmol Vis Sci.* 1999;40:2100-2105.
- Berkowitz BA, McDonald C, Ito Y, Tofts PS, Latif Z, Gross J. Measuring the human retinal oxygenation response to a hyperoxic challenge using MRI: eliminating blinking artifacts and demonstrating proof of concept. *Magn Reson Med.* 2001;46:412-416.
- Berkowitz BA, Zhang W. Significant reduction of the panretinal oxygenation response after 28% supplemental oxygen recovery in experimental ROP. *Invest Ophthalmol Vis Sci.* 2000;41:1925-1931.
- Berson EL, Remulla JE, Rosner B, Sandberg MA, Weigel-DiFranco C. Evaluation of patients with retinitis pigmentosa receiving electric stimulation, ozonated blood, and ocular surgery in Cuba [see comments]. *Arch Ophthalmol.* 1996;114:560-563.
- Bertram B, Wolf S, Fiehöfer S, Schulte K, Arend O, Reim M. Retinal circulation times in diabetes mellitus type 1. *Br J Ophthalmol.* 1991;75:462-465.
- Bignell J. Investigations into the blood supply of the optic nerve with special reference to the lamina cribrosa region. *Trans Ophthalmol Soc Aust.* 1952;12:105.
- Bill A, Sperber GO. Control of retinal and choroidal blood flow. *Eye.* 1990;4:319-325.
- Bioeffects Report Sub-Committee of the AIUM Bioeffects Committee. Bioeffects considerations for the safety of diagnostic ultrasound. *J Ultrasound Med.* 1988;7:S1-S38.
- Bischoff PM, Niederberger HJ, Torok B, Speiser P. Simultaneous indocyanine green and fluorescein angiography. *Retina.* 1995;15:91-99.
- Blair NP, Fekke GT, Morales-Stopello J, et al. Prolongation of the retinal mean circulation time in diabetes. *Arch Ophthalmol.* 1982;100:764-768.
- Boker T, Fang T, Steinmetz R. Refractive error and choroidal perfusion characteristics in patients with choroidal neovascularization and age-related macular degeneration. *Ger J Ophthalmol.* 1993;2:10-13.
- Borgos JA. TSF's LDV blood flowmeter. In: Shepherd AP, Öberg PA, eds. *Laser-Doppler Flowmetry*. Boston: Kluwer Academic Publishers; 1989:73-92.
- Bosem ME, Lusky M, Weinreb RN. Short-term effects of levobunolol on ocular pulsatile flow. *Am J Ophthalmol.* 1992;114:280-286.
- Bracher D, Dozzi M, Lotmar W. Measurement of vessel width on fundus photographs. *Graefes Arch Clin Exp Ophthalmol.* 1979;21:35-48.
- Bressler N, Munoz B, Maguire MG, et al. Five-year incidence and disappearance of drusen and retinal pigment epithelial abnormalities. Waterman study. *Arch Ophthalmol.* 1995;113:301-308.
- Brinckmann-Hansen O, Engvold O. Microphotometry of the blood column and the light streak on retinal vessels in fundus photographs. *Acta Ophthalmol Suppl.* 1986;179:9-19.
- Bulpitt CJ, Dollery CT. Estimation of retinal blood flow by measurement of mean circulation time. *Cardiovasc Res.* 1971;5:406-412.
- Bulpitt CJ, Dollery CT, Kohner EM. The marginal plasma zone in the retinal microcirculation. *Cardiovasc Res.* 1970;4:207.
- Burk RO, Rohrschneider K, Takamoto T, et al. Laser scanning tomography and stereophotogrammetry in three-dimensional optic disc analysis. *Graefes Arch Clin Exp Ophthalmol.* 1993;231:193-198.
- Bursell S, Clermont A, Kinsley BT, Simonson DC, Aiello LM, Wolpert H. Retinal blood flow changes in patients with insulin-dependent diabetes mellitus and no diabetic retinopathy. *Invest Ophthalmol Vis Sci.* 1996;37:886-897.
- Bursell S, Clermont A, Oren B, King G. The in vivo effect of endothelins on retinal circulation in nondiabetic and diabetic rats. *Invest Ophthalmol Vis Sci.* 1995;36:596-607.
- Butt ZA, McKillop G, O'Brien C. Measurement of ocular blood flow velocity using Color Doppler imaging in low tension glaucoma. *Eye.* 1995;9:29-33.
- Centofanti M, Bonini S, Manni G, Guinetti-Neuschuler C, Bucci MG, Harris A. Do sex and hormonal status influence choroidal circulation? *Br J Ophthalmol.* 2000;84:786-787.
- Chakrabarti S, Cukiernik M, Hileeto D, Evans T, Chen S. Role of vasoactive factors in the pathogenesis of early changes in diabetic retinopathy. *Diabetes Metab Res Rev.* 2000;16:393-407. Review.
- Chakravarthy U, Gardiner T, Anderson P, Archer D, Trimble E. The Effect of endothelin 1 on the retinal microvascular pericyte. *Microvasc Res.* 1992;43:241-254.
- Chang BY, Hee WC, Ling R, Broadway DC, Beigi B. Local anaesthetic techniques and pulsatile ocular blood flow. *Br J Ophthalmol.* 2000;84:1260-1263.
- Chang EJ, Fanous MM, Jocson VL. Reproducibility of ophthalmic artery blood flow analysis with transcranial Doppler flow spectrum vs. linear color Doppler imaging. ARVO Abstract. *Invest Ophthalmol Vis Sci.* 1994;35(suppl):1658.
- Chen SJ, Cheng CY, Lee AF, et al. Pulsatile ocular blood flow in asymmetric exudative age related macular degeneration. *Br J Ophthalmol.* 2001;85:1411-1415.
- Chen J, Fitzke F, Pauleikhoff D, Bird AC. Functional loss in age-related Bruch's membrane change with choroidal perfusion defect. *Invest Ophthalmol Vis Sci.* 1992;33:334-340.
- Chen J, Graham S, Nakayama M, et al. Apoptosis repressor genes Bcl-2 and Bcl-x-long are expressed in the rat brain following global ischemia. *J Cereb Blood Flow Metab.* 1997;19:2-10.
- Christ TH, Stodtmeister R, Pillunat L. Okulo-oszillo-dynamographie nach ulrich: erste ergebnisse bei carotisstenosen. *Klin Monatsbl Augenheilkd.* 187:256-261.
- Chung HS, Harris A, Evans DW, Kagemann L, Garzozzi HJ, Martin B. Vascular aspects in the pathophysiology of

- glaucomatous optic neuropathy. *Surv Ophthalmol.* 1999;43(suppl 1):S43-50. Review.
- Chung HS, Harris A, Kagemann L, Martin B. Peripapillary retinal blood flow in normal tension glaucoma. *Br J Ophthalmol.* 1999;83:466-469.
- Cioffi GA, Van Buskirk EM. Microvasculature of the anterior optic nerve. *Surv Ophthalmol.* 1994;38(suppl):S107.
- Cioffi GA, Wang L. Optic nerve blood flow in glaucoma. *Semin Ophthalmol.* 1999;14:164-170. Review.
- Cioffi GA. Three common assumptions about ocular blood flow and glaucoma. *Surv Ophthalmol.* 2001;45(suppl 3):S325-31; discussion S332-334. Review.
- Ciulla TA. Evolving pathophysiological paradigms for age related macular degeneration. *Br J Ophthalmol.* 2001 May;85:510-512.
- Ciulla TA, Harris A, Chung HS, et al. Color Doppler imaging discloses reduced ocular blood flow velocities in nonexudative age-related macular degeneration. *Am J Ophthalmol.* 1999;128:75-80.
- Ciulla TA, Harris A, Kagemann L, et al. Choroidal perfusion perturbations in non-neovascular age related macular degeneration. *Br J Ophthalmol.* 2002 Feb;86:209-213.
- Ciulla TA, Harris A, Martin BJ. Ocular perfusion and age-related macular degeneration. *Acta Ophthalmol Scand.* 2001;79:108-115. Review.
- Clermont AC, Aiello LP, Mori F, Aiello LM, Bursell SE. Vascular endothelial growth factor and severity of nonproliferative diabetic retinopathy mediate retinal hemodynamics in vivo: a potential role for vascular endothelial growth factor in the progression of nonproliferative diabetic retinopathy [see comments]. *Am J Ophthalmol.* 1997;124:433-446.
- Emelo J, Strmen P, Krasnik V. Evaluation of circulatory flow in vessels of the eye and orbit using color duplex ultrasonography. *Ceska Slov Oftalmol.* 1996;52:372-378.
- Coscas G, Gaudric A. Natural course of nonaphakic cystoid macular edema. *Surv Ophthalmol.* 1984;28(suppl):471-484.
- Costa VP, Harris A. CDI of ophthalmic artery blood flow in patients with TIAs [letter]. *Ophthalmology.* 1996;103:993-994.
- Cranstoun SD, Petrig BL, Riva CE, Baine J. Optic nerve head blood flow in the human eye by laser Doppler flowmetry (LDF). ARVO Abstracts. *Invest Ophthalmol Vis Sci.* 1994;35:1658.
- Cruickshanks KJ, Klein R, Klein BE. Sunlight and age-related macular degeneration: the Beaver Dam Eye Study. *Arch Ophthalmol.* 1993;111:514-518.
- Cunha-Vaz JG, Fonseca JR, de Abreu JRF, Lima JJP. Studies on retinal blood flow: II. Diabetic retinopathy. *Arch Ophthalmol.* 1978;96:809-811.
- Cunha-Vaz JG, Lima JJP. Studies on retinal blood flow: I. Estimation of human retinal blood flow by slit-lamp fluorophotometry. *Arch Ophthalmol.* 1978;96:893-897.
- Dahl-Jorgensen K. Diabetic microangiopathy. *Acta Paediatr Suppl.* 1998;425:31-34.
- Damon DN, Duling DR. A comparison between mean blood velocities and center-line red-cell velocities as measured with a mechanical image streaking velocimeter. *Microvasc Res.* 1979;17:330-332.
- Danser A, Derkx F, Admiraal P, et al. Angiotensin levels in the eye. *Invest Ophthalmol Vis Sci.* 1994;35:1008-1018.
- Danser A, Vandendorpel M, Deinum J, et al. Renin, prorenin, and immunoreactive renin in vitreous fluid from eyes with and without diabetic retinopathy. *J Clin Endocrinol Metab.* 1989;68:106-167.
- Davies EG, Sullivan PM, Fitzpatrick M, Kohner EM. Validations and reproducibility of laser Doppler velocimetry for the measurement of retinal blood flow. *Curr Eye Res.* 1992;11:633-640.
- De La Rubia G, Oliver F, Inoguchi T, King G. Induction of resistance to endothelin-1's biochemical actions by elevated glucose levels in retinal pericytes. *Diabetes.* 1992;41:1533-1539.
- Delori FC, Fitch KA, Fekete GT, Deupree DM, Weiter JJ. Evaluation of micrometric and microdensitometric methods for measuring the width of retinal vessel image on fundus photographs. *Graefes Arch Clin Exp Ophthalmol.* 1988;226:393-399.
- Denninghoff KR, Smith MH, Hillman LW, Redden D, Rue LW. Retinal venous oxygen saturation correlates with blood volume. *Acad Emerg Med.* 1998;56:577-582.
- Drance SM. Some factors in the production of low tension glaucoma. *Br J Ophthalmol.* 1972;56:229-237.
- Duijm HF, Van den Berg TJ, Greve EL. A comparison of retinal and choroidal hemodynamics in patients with primary open angle glaucoma and normal pressure glaucoma. *Am J Ophthalmol.* 1997;123:644-656.
- Durcan FJ, Flaherty PM, Digre KB, Lundergan MK. Use of color Doppler imaging to assess ocular blood flow in low tension glaucoma. ARVO Abstract. *Invest Ophthalmol Vis Sci.* 1993;34(suppl):1388.
- Eagle RJ. Mechanisms of maculopathy. *Ophthalmology.* 1984;91:613-625.
- Eberli B, Riva CE, Fekete GT. Mean circulation time of fluorescence in retinal vascular segments. *Arch Ophthalmol.* 1979;97:145-148.
- Eisenlohr JE, Langham ME. The relationship between pressure and volume changes in living and dead rabbit eyes. *Invest Ophthalmol.* 1962;1:63-77.
- Eisenlohr JE, Langham ME, Maumenee AE. Manometric studies of the pressure-volume relationship in living and enucleated eyes of individual human subjects. *Br J Ophthalmol.* 1962;46:536-548.
- Emery JK, Landis D, Paton D. The lamina cribrosa in normal and glaucomatous eyes. *Trans Am Acad Ophthalmol Otolaryngol.* 1974;78:290.
- Erikson SJ, Hendrix LE, Massaro BM, et al. Color Doppler flow imaging of the normal and abnormal orbit. *Radiology.* 1989;173:511-516.
- Ernest JT, Potts AM. Pathophysiology of the distal portion of the optic nerve: 2. Vascular relationships. *Am J Ophthalmol.* 1968;66:380.
- Esgin H, Alimgil ML, Erda S. The effect of systemic hypertension on pulsatile ocular blood flow in diabetic patients. *Acta Ophthalmol Scand.* 2001;79:160-162.
- Evans DW, Harris A, Danis RP, Arend O, Martin BJ. Altered retrobulbar vascular reactivity in early diabetic retinopathy. *Br J Ophthalmol.* 1997;81:279-282.
- Fallon TJ, Chowienzyk P, Kohner EM. Measurement of retinal blood flow in diabetes by the blue-light entoptic phenomenon. *Br J Ophthalmol.* 1986;70:43-46.
- Fallon TJ, Maxwell D, Kohner EM. Measurement of autoregulation of retinal blood flow using the blue field

- entoptic phenomenon. *Trans Ophthalmol Soc UK*. 1985;104:857-860.
- Fallon TJ, Maxwell D, Kohner EM. Retinal vascular autoregulation in conditions of hyperoxia and hypoxia using the blue field entoptic phenomenon. *Ophthalmology*. 1985;92:701-705.
- Fallon TJ, Maxwell DL, Kohner EM. Autoregulation of retinal blood flow in diabetic retinopathy measured by the blue-light entoptic technique. *Ophthalmology*. 1987;94:1410-1415.
- Felke G, Delori F, Webb R. Beam steering optical system and method and ophthalmic apparatus using same having spaced apart irradiation and observation paths. US patent 5,633,695. 1997;5:695.
- Felke GT, Buzney SM, Ogasawara H, et al. Retinal circulatory abnormalities in type 1 diabetes. *Invest Ophthalmol Vis Sci*. 1994;35:2968-2975.
- Felke GT, Green GJ, Goger DG, McMeel JW. Laser Doppler measurements of the effect of panretinal photocoagulation on retinal blood flow. *Ophthalmology*. 1982;89:757-762.
- Felke GT, Ishiko S, McMeel JW. Evaluation of a new laser Doppler retinal blood flowmeter [ARVO abstract]. *Invest Ophthalmol Vis Sci*. 1999;40:S487. Abstract 2570.
- Felke GT, Riva CE. Laser Doppler measurements of blood velocity in human retinal vessels. *J Opt Soc Am*. 1978;68:526-531.
- Felke GT, Tagawa H, Deupree DM, Goger DG, Sebag J, Weiter JJ. Blood flow in the normal human retina. *Invest Ophthalmol Vis Sci*. 1989;30:58-65.
- Felke GT, Tagawa H, Yoshida A, et al. Retinal circulatory changes related to retinopathy progression in insulin-dependent diabetes mellitus. *Ophthalmology*. 1985;92:1517-1522.
- Feman SS, Schaffer C, van Heuven WJ. Advances in TV-fluoroangiography. *Doc Ophthalmol*. 1976;9:19-23.
- Fercher AF. In vivo measurement of fundus pulsation by laser interferometry. *IEEE Trans Biomed Eng*. 1984;20:1469-1471.
- Ferrari-Dileo G, Davis E, Anderson D. Glaucoma, capillaries, and pericytes: 3. Peptide hormone binding and influence on pericytes. *Ophthalmologica*. 1996;210:269-275.
- Ferrari-Dileo G, Ryan J, Rockwood E, et al. Angiotensin-converting enzyme in bovine, feline, and human ocular tissues. *Invest Ophthalmol Vis Sci*. 1988;29:876-881.
- Ferrari-Dileo G, Davis E, Anderson D. Angiotensin binding sites in bovine and human retinal blood vessels. *Invest Ophthalmol Vis Sci*. 1987;28:1747-1751.
- Ferrari-Dileo G, Davis EB, Anderson DR. Angiotensin II binding receptors in retinal and optic nerve head blood vessels. *Invest Ophthalmol Vis Sci*. 1991;32:21-26.
- Ffytche T, Bulpitt C, Kohner E, Archer D, Dollery C. Effect of changes in intraocular pressure on the retinal microcirculation. *Br J Ophthalmol*. 1974;58:514-522.
- Findl O, Rainer G, Dallinger S, et al. Assessment of optic disk blood flow in patients with open-angle glaucoma. *Am J Ophthalmol*. 2000;130:589-596.
- Flaharty PM, Priest DL, Eaton AM, et al. Reproducibility of orbital hemodynamic parameters as measured by color Doppler imaging in normal volunteers. ARVO Abstract. *Invest Ophthalmol Vis Sci*. 1994;35(suppl):1630.
- Flaharty PM, Sergott RC, Lieb W, et al. Optic nerve sheath decompression may improve blood flow in anterior ischemic optic neuropathy. *Ophthalmology*. 1993;100:297-305.
- Flaharty P, Phillips W, Sergott RC, Stefanyshyn M, Bosley T, Savino PJ. Color Doppler imaging of superior ophthalmic vein thrombosis. *Arch Ophthalmol*. 1991;109:582-583.
- Flammer J, Haefliger IO, Orgul S, Resink T. Vascular dysregulation: a principal risk factor for glaucomatous damage? *J Glaucoma*. 1999;8:212-219. Review.
- Flammer J, Pache M, Resink T. Vasospasm, its role in the pathogenesis of diseases with particular reference to the eye. *Prog Retin Eye Res*. 2001;20:319-349. Review.
- Flanagan JG, Hutchings N, Liu H, Hosking SL, Ethier CR. A new method to monitor glaucomatous progression: canny edge detection of scanning laser tomography (SLT) images of the optic nerve head. [Arvo Abstract] *IOVS*. 2000;41:s121.
- Fontana L, Poinsoosawmy D, Bunce CV, O'Brien C, Hitchings RA. Pulsatile ocular blood flow investigation in asymmetric normal tension glaucoma and normal subjects. *Br J Ophthalmol*. 1998;82:731-736.
- Freeman W, Lerner C, Mines JA, et al. A prospective study of the ophthalmologic findings in the acquired immune deficiency syndrome. *Am J Ophthalmol*. 1984;97:133-142.
- Friedlander S, DeMaio R, Sinclair S, Werner E. The acute effects of betaxolol on human macular hemodynamics in normals. ARVO Abstract. *Invest Ophthalmol Vis Sci*. 1992;33(suppl):810.
- Friedman E. A hemodynamic model of the pathogenesis of age-related macular degeneration. *Ophthalmology*. 1997;124:677-682.
- Friedman E, Krupsky S, Lane AM, et al. Ocular blood flow velocity in age-related macular degeneration. *Ophthalmology*. 1995;102:640-646.
- Gabel VP, Birngruber R, Nasemann J. The scanning laser ophthalmoscope and its use as a fluorescein angiography instrument. *Fortschritte der Ophthalmologie*. 1988;85:569-573.
- Galassi F, Nuzzaci G, Sodi A, et al. Color Doppler imaging in evaluation of optic nerve blood supply in normal and glaucomatous subjects. *Int Ophthalmol*. 1992;16:273-276.
- Galin MA, Baras I, Best M, et al. Methods of suction ophthalmodynamometry. *Ann Ophthalmol*. 1970;2:439.
- Garcia CR, Rivero ME, Bartsch DU, et al. Oral fluorescein angiography with the confocal scanning laser ophthalmoscope. *Ophthalmology*. 1999;106:1114-1118.
- Garzozzi HJ, Shoham N, Chung HS, Kagemann L, Harris A. Ocular blood flow measurements and their importance in glaucoma and age-related macular degeneration. *Isr Med Assoc J*. 2001;3:443-448. Review.
- Gasser P. Why study vascular factors in glaucoma? *Int Ophthalmol*. 1998;99:22:221-225. Review.
- Gasser P, Flammer J, Guthauser U, Mahler F. Do vasospasms provoke ocular diseases? *Angiology*. 1990;41:213-219.
- Geijssen HC. *Studies on Normal Pressure Glaucoma*. New York: Kugler; 1991:8-31.
- Gekkiewa M, Orgul S, Gherghel D, Gugleta K, Prunte C, Flammer J. The influence of sex difference in measurements with the Langham Ocular Blood Flow System. *Jpn J Ophthalmol*. 2001;45:528-532.
- Gentry LR. Anatomy of the orbit. *Neuroimaging Clin N Am*. 1998;8:171-194. Review.
- Geyer O, Neudorfer M, Snir T, et al. Pulsatile ocular blood flow in diabetic retinopathy. *Acta Ophthalmol Scand*. 1999;77:522-525.

- Giers U, Pillunat LE, Stodtmeister R, Prang J. Iris fluorescence angiography findings in oculo-oscillodynamography. *Klinische Monatsblätter für Augenheilkunde*. 1991;199:267-273.
- Gillardot F, Lenz C, Waschke KI, et al. Altered expression of Bcl-2, Bcl-x, Bax, and c-Fos colonizes with DNA fragmentation and ischemic cell damage following middle cerebral artery occlusion in rats. *Brain Res Mol Brain Res*. 1996;40:254-260.
- Glasgow B, Weisberger A. A quantitative and cartographic study of retinal microvasculopathy in acquired immunodeficiency syndrome. *Am J Ophthalmol*. 1994;118:46-56.
- Göbel W, Lieb WE. Changes in orbital hemodynamics caused by nitroglycerin and nifedipine. *Ophthalmologie*. 1995;92:206-211.
- Göbel W, Lieb WE, Ho A, Sergott RC. Color Doppler ultrasound: a new procedure in the study of orbital blood vessels in diabetic retinopathy. *Ophthalmologie*. 1994;91:26-30.
- Goebel W, Lieb WE, Ho A, Sergott RC, Farhoumand R, Grehn E. Color Doppler imaging: a new technique to assess orbital blood flow in patients with diabetic retinopathy. *Invest Ophthalmol Vis Sci*. 1995;36:864-870.
- Gowers WR. The state of the arteries in Bright's disease. *Br Med J*. 1876;2:743-745.
- Granstam E, Wang L, Bill A. Ocular effects of endothelin-1 in the cat. *Curr Eye Res*. 1994;11:325-332.
- Grunwald JE. Effect of topical carteolol on the normal human retinal circulation. *Invest Ophthalmol Vis Sci*. 1992;33:1853-1856.
- Grunwald JE. Effect of topical timolol on the human retinal circulation. *Invest Ophthalmol Vis Sci*. 1986;27:1713-1719.
- Grunwald JE. Effect of two weeks of timolol maleate treatment on the normal retinal circulation. *Invest Ophthalmol Vis Sci*. 1991;32:39-45.
- Grunwald JE, Brucker AJ, Grunwald SE, Riva CE. Retinal hemodynamics in proliferative diabetic retinopathy: a laser Doppler velocimetry study. *Invest Ophthalmol Vis Sci*. 1993;34:66-71.
- Grunwald JE, Furubayashi C. Effect of topical timolol maleate on the ophthalmic artery blood pressure. *Invest Ophthalmol Vis Sci*. 1989;30:1095-1100.
- Grunwald JE, Riva CE, Brucker AJ, Sinclair SH, Petrig BL. Altered retinal vascular reactivity to 100% oxygen breathing in diabetes mellitus. *Ophthalmology*. 1984;91:1447-1452.
- Grunwald JE, Riva CE, Brucker AJ, Sinclair SH, Petrig BL. Effect of pan-retinal photocoagulation on retinal blood flow in proliferative diabetic retinopathy. *Ophthalmology*. 1986;93:590-595.
- Grunwald JE, Riva CE, Martin DB, Quint AR, Epstein PA. Effect of an insulin-induced decrease in blood glucose on the human diabetic retinal circulation. *Ophthalmology*. 1987;94:1614-1620.
- Grunwald JE, Riva CE, Sinclair SH, Brucker AJ, Petrig BL. Laser Doppler velocimetry study of retinal circulation in diabetes mellitus. *Arch Ophthalmol*. 1986;104:991-996.
- Grunwald JE, Riva CE, Stone RA, et al. Retinal autoregulation in open-angle glaucoma. *Ophthalmology*. 1984;91:1690-1694.
- Grunwald JE, Sinclair SH, Riva CE. Autoregulation of the retinal circulation in response to decrease of intraocular pressure. *Invest Ophthalmol Vis Sci*. 1982;23:124-127.
- Grunwald JE, Zinn H. The acute effect of oral acetazolamide on macular blood flow. *Invest Ophthalmol Vis Sci*. 1992;33:504-507.
- Grunwald JE, Riva CE, Petrig BL, Sinclair SH, Brucker AJ. Effect of pure O₂-breathing on retinal blood flow in normals and in patients with background diabetic retinopathy. *Curr Eye Res*. 1984;3:239-241.
- Gutloff RE, Berger RW, Winkler P, et al. Doppler ultrasonography of the ophthalmic and central retinal vessels. *Arch Ophthalmol*. 1991;109:532-536.
- Gutloff RE, Berger RW, Winkler P, et al. Doppler ultrasonography of malignant melanomas of the uvea. *Arch Ophthalmol*. 1991;109:537-541.
- Güven D, Özdemir H, Hasanreisoglu B. Hemodynamic alterations in diabetic retinopathy. *Ophthalmology*. 1996;103:1245-1249.
- Guyon DR, Yannuzzi LA, Slakter JS, et al. Classification of choroidal neovascularization by digital indocyanine green videoangiography. *Ophthalmology*. 1996;103:2054-2060.
- Haefliger IO, Flammer J, Beny JL, Luscher TF. Endothelium-dependent vasoactive modulation in the ophthalmic circulation. *Prog Retin Eye Res*. 2001;20:209-225. Review.
- Haefliger IO, Flammer J, Luscher T. Nitric oxide and endothelin-1 are important regulators of human ophthalmic artery. *Invest Ophthalmol Vis Sci*. 1992;33:2340-2343.
- Haefliger IO, Lietz A, Griesser SM, et al. Modulation of Heidelberg Retinal Flowmeter parameter flow at the papilla of healthy subjects: effect of carbogen, oxygen, high intraocular pressure, and beta-blockers. *Surv Ophthalmol*. 1999;43(suppl 1):S59-65.
- Haefliger I, Meyer P, Flammer J, Luscher T. The Vascular endothelium as a regulator of the ocular circulation: a new concept in ophthalmology? *Surv Ophthalmol*. 1994;39:123-132.
- Haessler FH, Squier TL. Measurements of retinal vessels in early hypertension. *Trans Am Ophthalmol Soc*. 1931;29:254-262.
- Haller A. Arteriarum oculi historia et tabulae arteriarum oculi. Göttingen, 1754. Cited by Francois et al in *Br J Ophthalmol*. 1954;38:472.
- Hardy P, Dumont I, Bhattacharya M, et al. Oxidants, nitric oxide and prostanooids in the developing ocular vasculature: a basis for ischemic retinopathy. *Cardiovasc Res*. 2000;47:489-509. Review.
- Harino S, Riva CE, Petrig BL. Intravenous nicardipine in cats increases optic nerve head but not retinal blood flow. *Invest Ophthalmol Vis Sci*. 1992;33:2885-2890.
- Harris A, Anderson DR, Pillunat L, et al. Laser Doppler flowmetry measurement of changes in human optic nerve head blood flow in response to blood gas perturbations. *J Glaucoma*. 1996;5:258-265.
- Harris A, Arend O, Kopecky K, et al. Physiological perturbation of ocular and cerebral blood flow as measured by scanning laser ophthalmoscopy and color Doppler imaging. *Surv Ophthalmol*. 1994;38(suppl):S81-86.
- Harris A, Harris M, Biller J, et al. Aging affects the retrobulbar circulation differently in women and men. *Arch Ophthalmol*. 2000;118:1076-1080.
- Harris A, Kagemann L, Cioffi GA. Assessment of human ocular hemodynamics. *Surv Ophthalmol*. 1998;42:509-533. Review.
- Harris A, Martin BJ, Shoemaker JA. Regulation of retinal blood flow during blood gas perturbation. *J Glaucoma*. 1994;3(suppl 1):S82-S90.

- Harris A, Sergott RC, Spaeth GL, et al. Color Doppler analysis of ocular vessel blood velocity in normal tension glaucoma. *Am J Ophthalmol.* 1994;118:642-649.
- Harris A, Shoemaker JA, Burgoyne J, et al. The acute effect of topical beta-adrenergic antagonists on normal perimacular hemodynamics. *J Glaucoma.* 1995;4:36-40.
- Harris A, Arend O, Danis RP, Evans D, Wolf S, Martin BJ. Hyperoxia improves contrast sensitivity in early diabetic retinopathy. *Br J Ophthalmol.* 1996;80:209-213.
- Harrison D: The endothelial cell. *Heart Dis Stroke.* 1992;March/April:95-99.
- Hayreh SS. Blood flow in the optic nerve head and factors that may influence it. *Prog Retin Eye Res.* 2001;20:595-624. Review.
- Hayreh SS. The blood supply of the optic nerve head and the evaluation of it: myth and reality. *Prog Retin Eye Res.* 2001;20:563-593. Review.
- Hayreh SS. Inter-individual variation in the blood supply of the optic nerve head: its importance in various ischemic disorders of the nerve head, and glaucoma, low-tension glaucoma, and allied disorders. *Doc Ophthalmol.* 1985;59:217.
- Hayreh SS. Optic nerve head blood supply in health and disease. In: Lambrou GN, Greve EL, eds. *Ocular Blood Flow in Glaucoma.* Amsterdam: Kugler & Ghedini; 1989:3-49.
- Hayreh SS. Structure and blood supply of the optic nerve. In: Heilmann K, Richardson KT, eds. *Glaucoma: Conceptions of a Disease: Pathogenesis, Diagnosis, Therapy.* Stuttgart: Georg Thieme; 1978:78-96.
- Hayreh SS. Segmental nature of the choroidal vasculature. *Br J Ophthalmol.* 1975;59:631.
- Hayreh SS. Blood supply of the optic nerve head and its role in optic atrophy, glaucoma, and oedema of the optic disc. *Br J Ophthalmol.* 1969;53:721.
- Hayreh SS. The central artery of the retina—its role in the blood supply of the optic nerve. *Br J Ophthalmol.* 1963; 47:651.
- Hayreh SS. The orbital vessels of rhesus monkeys. *Exp Eye Res.* 1964;3:16.
- Hayreh SS. The ophthalmic artery: III. *Br J Ophthalmol.* 1962; 46:212.
- Hedges TR, Reichel E, Duker JS, et al. Color Doppler imaging identifies different mechanisms of central retinal artery occlusion. ARVO Abstract. *Invest Ophthalmol Vis Sci.* 1993;34(suppl):842.
- Henkind P, Levitzky M. Angioarchitecture of the optic nerve: 1. The papilla. *Am J Ophthalmol.* 1969;68:979.
- Hessemer V, Schmidt KG. Influence of panretinal photo-coagulation on the ocular pulse curve. *Am J Ophthalmol.* 1997;123:748-752.
- Hickam JB, Frayser R. A photographic method for measuring the mean retinal circulation time using fluorescein. *Invest Ophthalmol.* 1963;4:876-884.
- Hickam JB, Frayser RF. Studies of retinal circulation in man: observations on vessel diameter, arteriovenous oxygen difference, and mean circulation time. *Circulation.* 1966;33:302-314.
- Hickam JB, Sieker HO. Retinal vascular reactivity in patients with diabetes mellitus and with arteriosclerosis. *Circulation.* 1960;22:243-246.
- Hill DW. Ocular and retinal blood flow. *Acta Ophthalmol Suppl.* 1989;191:15-18.
- Hitchings R. The ocular pulse. *Br J Ophthalmol.* 1991;75:65.
- Ho AC, Lieb WE, Flaherty PM, et al. Color Doppler imaging of the ocular ischemic syndrome. *Ophthalmology.* 1992; 99:1453-1462.
- Ho A, Lieb W, Flaherty PM, et al. Color Doppler imaging of the ocular ischemic syndrome. *Ophthalmology.* 1992;99: 1453-1462.
- Hodge JV, Parr JC, Spears GFS. Comparison of method of measuring vessel widths on retinal photographs and the effect of fluorescein injection on apparent retinal vessel caliber. *Am J Ophthalmol.* 1969;68:1060-1068.
- Holland G, Pepose J, Pettit TH, Gottlieb MS, Yee RD, Foos RY. Acquired immune deficiency syndrome: ocular manifestations. *Ophthalmology.* 1983;90:859-873.
- Holz FG, Bellmann C, Dithmar S, Rohrschneider K, Burk RO, Volcker HE. [Simultaneous fluorescein and indocyanine green angiography with a confocal laser ophthalmoscope.] *Ophthalmologie.* 1997;94:348-353.
- Holz FG, Bellmann C, Rohrschneider K, Burk RO, Volcker HE. Simultaneous confocal scanning laser fluorescein and indocyanine green angiography. *Am J Ophthalmol.* 1998; 125:227-236.
- Hosking SL, Embleton SJ, Cunliffe IA. Application of a local search strategy improves the detection of blood flow deficits in neuroretinal rim of glaucoma patients using scanning laser Doppler flowmetry. *Br J Ophthalmol.* 2001;85:1298-1302.
- Ito Y, Berkowitz BA. MR studies of retinal oxygenation. *Vision Res.* 2001;41:1307-1311.
- Jabs D, Green W, Fox R, Polk BF, Bartlett JG. Ocular manifestations of acquired immune deficiency syndrome. *Ophthalmology.* 1989;96:1092-1099.
- Jonas JB, Guggenmoos-Holzmann I, Naumann GO. Cilioretinal arteries in large optic disks. *Ophthalmic Res.* 1988;20:269-274.
- Jonas JB, Gusek GC, Guggenmoos-Holzmann I, Naumann GO. Correlations of the neuroretinal rim area with ocular and general parameters in normal eyes. *Ophthalmic Res.* 1988;20:298-303.
- Jonas JB, Gusek GC, Guggenmoos-Holzmann I, Naumann GO. Variability of the real dimensions of normal human optic discs. *Graefes Arch Clin Exp Ophthalmol.* 1988;226: 332-336.
- Jonas JB, Gusek GC, Naumann GO. Optic disc morphometry in chronic primary open-angle glaucoma: I. Morphometric intrapapillary characteristics. *Graefes Arch Clin Exp Ophthalmol.* 1988;226:522-530.
- Jonescu-Cuypers CP, Chung HS, Kagemann L, et al. A new reliable method for neuroretinal rim blood flow measurements with the Heidelberg Retina Flowmeter in healthy volunteers. [ARVO Abstract]. *Invest Ophthalmol Vis Sci.* 1999;40:276. Abstract 1455.
- Jonescu-Cuypers CP, Chung HS, Kagemann L, Ishii Y, Zarfati D, Harris A. New neuroretinal rim blood flow evaluation method combining Heidelberg retina flowmetry and tomography. *Br J Ophthalmol.* 2001;85:304-309.
- Jonescu-Cuypers CP, Thumann G, Hilgers RD, et al. Long-term fluctuations of the normalised rim/disc area ratio quotient in normal eyes. *Graefes Arch Clin Exp Ophthalmol.* 1999;237:181-186.
- Joos KM, Pillunat LE, Knighton RW, et al. Reproducibility of laser Doppler flowmetry (LDF) measurements of the

- human optic nerve. ARVO Abstracts. *Invest Ophthalmol Vis Sci.* 1994;35:1659.
- Jung E, Keiswetter H, Körber N, Wolf S, Reim M, Müller G. Quantification of characteristic blood flow parameters in the vessels of the retina with a picture analysis system for video fluorescein angiograms: initial findings. *Graefes Arch Clin Exp Ophthalmol.* 1983;211:133-136.
- Kadonosono K, Itoh N, Nomura E, Ohno S. Capillary blood flow velocity in patients with idiopathic epiretinal membranes. *Retina.* 1999;19:536-539.
- Kagemann L, Harris A, Chung HS, Evans D, Buck S, Martin B. Heidelberg retinal flowmetry: factors affecting blood flow measurement. *Br J Ophthalmol.* 1998;82:131-136.
- Kagemann LE, Harris A, Cantor LB, Martin BJ. Heidelberg Retinal Flowmetry: the effect of angle of incidence on blood flow measurement. ARVO Abstract. *Invest Ophthalmol Vis Sci.* 1996;37(suppl):5265.
- Kergoat H, Faucher C. Effects of oxygen and carbogen breathing on choroidal hemodynamics in humans. *Invest Ophthalmol Vis Sci.* 1999;40:2906-2911.
- Khoobehi B, Aly OM, Schuele KM, et al. Determination of retinal blood velocity with respect to the cardiac cycle using laser-triggered release of liposome-encapsulated dye. *Lasers Surg Med.* 1990;10:469-475.
- Khoobehi B, Peyman GA. Fluorescent labeling of blood cells for evaluation of retinal and choroidal circulation. *Ophthalmic Surg Lasers.* 1999;30:140-145.
- Khoobehi B, Peyman GA, Niesman MR, Oncel M. Measurement of retinal blood velocity and flow rate in primates using a liposome-dye system. *Ophthalmology.* 1989;96:905-912.
- Kimura H, Kiryu J, Nishiwaki H, Ogura Y. Visualization of the retinal microvasculature and its cell-density with a cell-permeant fluorescent dye in vitro. ARVO Abstract. *Invest Ophthalmol Vis Sci.* 1994;35(suppl):1633.
- Köber N, Gesch M, Kiewewetter H, Reim M, Schmid-Schönbein H. Fernsehfluoreszenzangiographie der Retina Neue technische Aspekte. *Graefes Arch Clin Exp Ophthalmol.* 1980;213:65-70.
- Koelle JS, Riva CE, Petrig BL, Cranston SD. Depth of tissue sampling in the optic nerve head using laser Doppler velocimetry. *Lasers Med Sci.* 1993;8:49-54.
- Kohner EM, Hamilton AM, Saunders SJ, Sutcliffe BA, Bulpitt CJ. The retinal blood flow in diabetes. *Diabetologia.* 1975;11:27-33.
- Kohner EM, Patel V, Rassam SM. Role of blood flow and impaired autoregulation in the pathogenesis of diabetic retinopathy. *Diabetes.* 1995;44:603-607.
- Kokinakis DJ, Siebert JE, Kaufman DI, Pernicone JR. Evaluation of ophthalmic arteries is possible using MRI. ARVO Abstract. *Invest Ophthalmol Vis Sci.* 1994;35(suppl):1123.
- Königsreuther KA, Michelson G. Retinal hemodynamics in glaucoma. ARVO Abstract. *Invest Ophthalmol Vis Sci.* 1994;35(suppl):1842.
- Kothe AC, Lovasik JV. A parametric evaluation of retinal vascular perfusion pressure and visual neural function in man. *Electroencephalogr Clin Neurophysiol.* 1990;75:185-199.
- Koyama T, Matsuo N, Shimizu K, et al. Retinal circulation times in quantitative fluorescein angiography. *Graefes Arch Clin Exp Ophthalmol.* 1990;228:442-446.
- Krakau CET. Calculation of the pulsatile ocular blood flow. *Invest Ophthalmol Vis Sci.* 1992;33:2754-2756.
- Krebs W, Krebs I. *Primate Retina and Choroid Atlas of Fine Structure in Man and Monkey.* New York: Springer-Verlag; 1991:116-139.
- Krejcy K, Wolzt M, Kreuzer C, et al. Characterization of angiotensin-II effects on cerebral and ocular circulation by noninvasive methods. *Br J Clin Pharmacol.* 1997;43:501-508.
- Langham ME, Eisenlohr JE. A manometric study of the rate of fall of the intraocular pressure in living and dead eyes of human subjects. *Invest Ophthalmol.* 1963;2:72-82.
- Langham ME, Farrel R, Krakau T, Silver D. Ocular pulsatile blood flow, hypotensive drugs, and differential light sensitivity in glaucoma. In: Krieglstein GK, ed. *Glaucoma Update IV.* Berlin: Springer-Verlag; 1991:162-172.
- Langham ME, Farrell RA, O'Brien V, et al. Non-invasive measurement of pulsatile blood flow in the human eye. In: Lambrou GN, Greve EL, eds. *Ocular Blood Flow in Glaucoma.* Berkeley: Kugler & Ghedini; 1989:93-99.
- Langham ME, Farrell RA, O'Brien, et al. Blood flow in the human eye. *Acta Ophthalmologica.* 1989;191(suppl):9-13.
- Langham ME, Grebe R, Hopkins S, et al. Choroidal blood flow in diabetic retinopathy. *Exp Eye Res.* 1991;52:167-173.
- Langham ME, Romeiko WJ. The unfavorable action of timolol on ocular blood flow and vision in glaucomatous eyes. ARVO Abstract. *Invest Ophthalmol Vis Sci.* 1992;32:1046.
- Langham ME, Tomey KF. A clinical procedure for the measurement of ocular pulse-pressure relationship and the ophthalmic arterial pressure. *Exp Eye Res.* 1978;27:17-25.
- Langham ME. Ocular blood flow and visual loss in glaucomatous eyes. In: Krieglstein GK, ed. *Glaucoma Update III.* Berlin: Springer-Verlag; 1987:58-66.
- Lee C, Charles H, Smith RT, Peachey NS, Cunha-Vaz JG, Goldberg MF. Quantification of macular ischaemia in sickle cell retinopathy. *Br J Ophthalmol.* 1987;71:540-545.
- Leib S, Kim Y, Chow LL, Sheldon RA, Tauber MG. Reactive oxygen intermediates contribute to necrotic and apoptotic neuronal injury in an infant rat model of bacterial meningitis due to group B streptococci. *J Clin Invest.* 1996;98:2632-2639.
- Levitzky M, Henkind P. Angioarchitecture of the optic nerve: II Lamina Cribrosa. *Am J Ophthalmol.* 1969;68:986.
- Lieb WE. Color Doppler ultrasonography of the eye and orbit. *Curr Opin Ophthalmol.* 1993;4:68-75.
- Lieb WE, Cohen SM, Merton DA, et al. Color Doppler imaging of the eye and orbit: technique and normal vascular anatomy. *Arch Ophthalmol.* 1991;109:527-531.
- Lieb WE, Flaharty PM, Ho A, Sergott RC. Color Doppler imaging of the eye and orbit: a synopsis of a 400 case experience. *Acta Ophthalmologica Suppl.* 1992;204:50-54.
- Lieb W, Flaharty P, Sergott RC, et al. Color Doppler imaging provides accurate assessment of orbital blood flow in occlusive carotid artery disease. *Ophthalmology.* 1991;98:548-552.
- Lieb WE, Shields JA, Cohen SM, et al. Color Doppler imaging in the management of intraocular tumors. *Ophthalmology.* 1990;97:1660-1664.
- Lieberman MF, Maumenee AE, Green WR. Histologic studies of the vasculature of the anterior optic nerve. *Am J Ophthalmol.* 1976;82:405.

- Littmann H. Zur Bestimmung der wahren Grösse eines Objekts auf dem Hintergrund des lebenden Auges. *Klin Monatsbl Augenheilkd.* 1982;180:286-289.
- Lofli K, Grunwald JE. The effect of caffeine on the human macular circulation. *Invest Ophthalmol Vis Sci.* 1991;32:3028-3032.
- Lu N, Shimura M, Kinukawa Y, Yoshida M, Tamai M. Quantitative analysis of leukocyte dynamics in retinal microcirculation of rats with short-term ischemia-reperfusion injury. *Curr Eye Res.* 1999;19:403-410.
- Macaya A. Apoptosis in the nervous system. *Rev Neurol.* 1996;24:1356-1360.
- Maccumber MW, Jampel HD, Snyder SH. Ocular effects of the endothelins: abundant peptides in the eye. *Arch Ophthalmol.* 1991;109:705-709.
- Mansberger S, Harris A, Caldemeyer K, et al. Acute effect of topical apraclonidine on perimacular and orbital hemodynamics. ARVO Abstract. *Invest Ophthalmol Vis Sci.* 1994;35(suppl):2176.
- Mares-Perlman J, Brady W, Klein R, Van den Langenberg GM, Klein BE, Palta M. Dietary fat and age related maculopathy [see comments]. *Arch Ophthalmol.* 1995;113:743-748.
- Mares-Perlman J, Brady W, Klein R, et al. Serum antioxidants and age related macular degeneration in a population based case control study. *Arch Ophthalmol.* 1995;113: 1518-1523.
- Martin XD, Rabineau PA. Vasoconstrictive effect of topical timolol on human retinal arteries. *Graefes Arch Clin Exp Ophthalmol.* 1989;27:526-530.
- Masaoka N, Nakaya K, Koura Y, Ohsaki M. Hemodynamic changes in two patients with retinal circulatory disturbances shown by fluorescein angiography using a scanning laser ophthalmoscope. *Retina.* 2001;21:155-160.
- Maumenee AE. Causes of optic nerve damage in glaucoma. *Ophthalmology* 90:741-752, 1983.
- Mendivil A. Ocular blood flow velocities in patients with proliferative diabetic retinopathy after panretinal photocoagulation. *Surv Ophthalmol.* 1997;42(Suppl 1):S89-S95.
- Mendivil A, Cuartero V. Ocular blood flow velocities in patients with proliferative diabetic retinopathy after scatter photocoagulation. Two years of follow-up. *Retina.* 1996;16:222-227.
- Mendivil A, Cuartero V, Mendivil M. Ocular blood flow velocities in patients with proliferative diabetic retinopathy and healthy volunteers: a prospective study. *Br J Ophthalmol.* 1995;79:413-416.
- Meyer P, Flammer J, Luscher T. Endothelium-dependent regulation of the ophthalmic microcirculation in the perfused porcine eye: role of nitric oxide and endothelins. *Invest Ophthalmol Vis Sci.* 1993;34:3614-3621.
- Meyer P, Flammer J, Luscher T. Local action of the renin angiotensin system in the porcine ophthalmic circulation: effects of ACE-inhibitors and angiotensin receptor antagonists. *Invest Ophthalmol Vis Sci.* 1995;36:555-562.
- Michelson G, Schmauss B. Two-dimensional mapping of the perfusion of the retina and optic nerve head. *Br J Ophthalmol.* 1995;79:1126-1132.
- Milbocker MT, Feke GT, Goger DG. Laser Doppler velocimetry stabilized in one dimension. *IEEE Trans Biomed Eng.* 1991; 38:928-930. Erratum. 1992;39:206.
- Minckler DS. Histology of optic nerve damage in ocular hypertension and early glaucoma. *Surv Ophthalmol.* 1989;33:401.
- Minckler DS, Spaeth GL. Optic nerve damage in glaucoma. *Surv Ophthalmol.* 1981;26:128-148.
- Mittl RN, Tiwari R, Wilkes E. Blue field entoptoscopy in diabetic retinopathy. *Indian J Ophthalmol.* 1990;38:10-13.
- Mitra RA, Sergott RC, Flaharty PM, et al. Optic nerve decompression improves hemodynamic parameters in papilledema. *Ophthalmology.* 1993;100:987-997.
- Moore RE. The retinitis of arterio-sclerosis and its relation to renal retinitis and to cerebral vascular disease. *Quart J Med.* 1916; 10:29-77.
- Morgan A, Hosking S. Ocular blood flow tonometer reproducibility: the effect of operator experience and mode of application. *Ophthalmic Physiol Opt.* 2001;21:401-406.
- Mori E, Konno S, Hikichi T, Yamaguchi Y, Ishiko S, Yoshida A. Factors affecting pulsatile ocular blood flow in normal subjects. *Br J Ophthalmol.* 2001;85:529-530.
- Mori E, Konno S, Hikichi T, Yamaguchi Y, Ishiko S, Yoshida A. Pulsatile ocular blood flow study: decreases in exudative age related macular degeneration. *Br J Ophthalmol.* 2001; 85:531-533.
- Morone G, Tazzi A, Carella G. [Examination of the venous system of the uvea (author's transl)]. *Klin Monatsbl Augenheilkd.* 1977;170:546-553.
- Munk P, Downey D, Nicolle D, et al. The role of colour flow Doppler ultrasonography in the investigation of disease in the eye and orbit. *Can J Ophthalmol.* 1993;4:171-176.
- Nagel, E, Vilser W, Lindloh C, Klein S. [Measuring retinal vascular diameter using the scanning laser ophthalmoscope and computer. Initial results.] *Ophthalmologie.* 1992;89:432-436.
- Nakahashi K. Macular blood flow measured by blue field entoptic phenomenon. *Jpn J Ophthalmol.* 1990;24:331-337.
- Nasemann JE, Müller M. Scanning laser angiography. In: Nasemann JE, Burk ROW, eds. *Scanning Laser Ophthalmoscopy and Tomography.* München: Quintessenz; 1990:63-80.
- Netland PA, Grosskreutz CL, Feke GT, Hart LJ. Color Doppler ultrasound analysis of ocular circulation after topical calcium channel blocker. *Am J Ophthalmol.* 1995;119:694-700.
- Newsome D, Green W, Miller ED, et al. Microvascular aspects of acquired immune deficiency syndrome. *Am J Ophthalmol.* 1984;98:590-601.
- Nickells R. Retinal ganglion cell death in glaucoma: the how, the why, and the maybe. *J Glaucoma.* 1996;5:345-356.
- Nicolela MT, Hnik P, Drance SM. Scanning laser Doppler flowmeter study of retinal and optic disk blood flow in glaucomatous patients. *Am J Ophthalmol.* 1996;122: 775-783.
- Niesel P, Gassman HB. Direkte fluorometrische Untersuchung am Augenhintergrund. *Ophthalmologica.* 1972;165: 297-302.
- Nilsson S. Nitric oxide as a mediator of parasympathetic vasodilation in ocular and extraocular tissues in the rabbit. *Invest Ophthalmol Vis Sci.* 1996;37:2110-2119.
- Nishiwaki H, Kimura H, Kiryu J, Ogura Y. Visualization and quantitative analysis of leukocyte dynamics in retinal microcirculation of rats. *Invest Ophthalmol Vis Sci.* 1996;37: 1341-1347.
- Novotny HR, Alvis DL. A method of photographing fluorescence in circulating blood in the human retina. *Circulation.* 1961;24:82-86.
- Öberg PA. Laser-Doppler flowmetry. *Crit Rev Biomed Eng.* 1990;18:125-163.
- Ohnishi Y, Fujisawa K, Ishibashi T, Kojima H. Capillary blood

- flow velocity measurements in cystoid macular edema with the scanning laser ophthalmoscope. *Am J Ophthalmol*. 1994;117:24-29.
- Okada AA, Mizusawa T, Sakai J, Usui M. Videofunduscopy and videoangiography using the scanning laser ophthalmoscope in Vogt-Koyanagi-Harada syndrome. *Br J Ophthalmol*. 1998;82:1175-1181.
- Okamoto N, Nishimura Y, Goami K, Harino S. [The effect of hyperbaric oxygen on ophthalmic artery blood velocity in patients with diabetic neuropathy.] *Nippon Ganka Gakkai Zasshi*. 1997;101:730-733.
- Oke H, Yamaguchi H, Sugiyama T, Al E. Retinal toxicity of nitric oxide released by administration of a nitric oxide donor in the albino rabbit. *Invest Ophthalmol Vis Sci*. 1997;38:2540-2544.
- Olver JM, Spalton DJ, McCartney ACE. Quantitative morphology of human retrolaminar optic nerve vasculature. *Invest Ophthalmol Vis Sci*. 1994;35:3858.
- Olver JM, Spalton DJ, McCartney ACE. Microvascular study of the retrolaminar optic nerve head in man: the possible significance in anterior ischaemic optic neuropathy. *Eye*. 1990;4:7.
- Onda E, Cioffi GA, Bacon DB, Van Buskirk EM. Microvasculature of the anterior human optic nerve. *Am J Ophthalmol*. 1995;120:92-102.
- Orgul S, Gugleta K, Flammer J. Physiology of perfusion as it relates to the optic nerve head. *Surv Ophthalmol*. 1999;43(suppl 1):S17-26. Review.
- Oyster CW. *The Human Eye: Structure and Function*. Sunderland, Mass: Sinauer Associates, Inc; 1999.
- Pakola SJ, Grunwald JE. Effects of oxygen and carbon dioxide on human retinal circulation. *Invest Ophthalmol Vis Sci*. 1993;34:2866-2870.
- Patel V, Rassam S, Newsom R, Wiek J, Kohner E. Retinal blood flow in diabetic retinopathy. *Brit Med J*. 1992;305:678-683.
- Pauleikhoff D, Chen J, Chisholm IH, Bird AC. Choroidal perfusion abnormality with age-related Bruch's membrane change. *Am J Ophthalmol*. 1990;109:211-217.
- Pepe J, Holland G, Nestor MS, Cochran AJ, Foos RY. Acquired immune deficiency syndrome. Pathogenic mechanisms of ocular disease. *Ophthalmology*. 1985;92:472-484.
- Petrig BL, Riva CE. Retinal laser Doppler velocimetry: towards its computer-assisted use. *Appl Optics*. 1988;27:1126-1134.
- Petrig BL, Riva CE, Cranston SD. Continuous real-time laser Doppler analysis system for ocular fundus flowmetry and velocimetry. ARVO Abstracts. *Invest Ophthalmol Vis Sci*. 1994;35:1402.
- Petrig BL, Riva CE, Hayreh SS. Laser Doppler flowmetry and optic nerve head blood flow. *Am J Ophthalmol*. 1999;127:413-425.
- Pichot O, Gonzalez B, Franco A, Mouillon M. Color Doppler ultrasonography in the study of orbital and ocular vascular diseases. *J Francais d Ophthalmologie*. 1996;19:19-31.
- Piguet B, Palmvang I, Chisholm IH, Minassian D, Bird AC. Evolution of age-related macular degeneration with choroidal perfusion abnormality. *Am J Ophthalmol*. 1992;113:657-663.
- Pillunat LE. Ocular blood flow endpoints. *Eur J Ophthalmol*. 1999;9(suppl 1):S44-47.
- Pillunat LE, Harris A, Anderson DR, Greve EL, eds. *Current Concepts on Ocular Blood Flow in Glaucoma*. The Hague. New York: Kugler; c1999.
- Pillunat LE, Lang GK, Harris A. The visual response to increased ocular blood flow in normal pressure glaucoma. *Surv Ophthalmol*. 1994;38(suppl):S139-147; discussion S147-148.
- Pillunat LE, Stodtmeister R. Effect of different antiglaucomatous drugs on ocular perfusion pressures. *J Ocul Pharmacol*. 1988;4:231-242.
- Pillunat LE, Stodtmeister R, Marquardt R, Mattern A. Ocular perfusion pressures in different types of glaucoma. *Int Ophthalmol*. 1989;13:37-42.
- Plesch A, Klingbeil U, Rappl W, Schrödel. Scanning ophthalmic imaging. In: Nasemann JE, Burk ROW, eds. *Scanning Laser Ophthalmoscopy and Tomography*. München: Quintessenz; 1990:23-33.
- Popma SE. Noninvasive assessment of the ocular circulation: color Doppler imaging. *J Am Optom Assoc*. 1995;66:123-128.
- Portellos M, Riva CE, Cranston SD, Petrig BL, Brucker AJ. Effects of adenosine on ocular blood flow. *Invest Ophthalmol Vis Sci*. 1995;36:1904-1909.
- Pourcelot L. Indications de l'ultrasonographie Doppler dans l'étude des vaisseaux périphériques. *Revue du Praticien*. 1975;25:4671-4680.
- Powis RL. Color flow imaging: understanding its science and technology. *J Diag Med Ultrasound*. 1988;4:236-245.
- Preussner PR, Richard G, Darrelmann O, Weber J, Kreissig I. Quantitative measurement of retinal blood flow in human beings by application of digital image-processing methods to television angiograms. *Graefes Arch Clin Exp Ophthalmol*. 1983;22:110-112.
- Prunte C. Indocyanine green angiographic findings in central serous chorioretinopathy. *Int Ophthalmol*. 1995;19:77-82.
- Prunte C, Flammer J. Choroidal capillary and venous congestion in central serous chorioretinopathy. *Am J Ophthalmol*. 1996;121:26-34.
- Prunte C, Flammer J. [Circulatory disorders of the choroid in patients with central serous chorioretinopathy]. *Klin Monatsbl Augenheilkd*. 1996;208:337-339.
- Prunte C, Orgul S, Flammer J. Abnormalities of microcirculation in glaucoma: facts and hints. *Curr Opin Ophthalmol*. 1998;9:50-55. Review.
- Quigley HA, Addicks EM. Regional differences in the structure of the lamina cribrosa and their relation to glaucomatous optic nerve damage. *Arch Ophthalmol*. 1981;99:137.
- Quigley H, Nickells R, Kerrigan LA, Pease ME, Thibault DJ, Zack DJ. Retinal ganglion cell death in experimental glaucoma and after axotomy occurs by apoptosis. *Invest Ophthalmol Vis Sci*. 1995;36:774-786.
- Radius RL, Gonzales M. Anatomy at the lamina cribrosa in human eyes. *Arch Ophthalmol*. 1981;99:2159.
- Ramachandran E, Frank R, Kennedy A. Effects of endothelin on cultured bovine retinal microvascular pericytes. *Invest Ophthalmol Vis Sci*. 1993;34:586-595.
- Ramallo PS, Dollery CT. Hypertensive retinopathy: caliber changes in retinal blood vessels following blood pressure reduction an inhalation of oxygen. *Circulation*. 1968;37:580-588.
- Rassam SMB, Patel V, Brinckmann-Hansen O, Engvold O, Kohner E. Accurate vessel width measurement from fundus photographs: a new concept. *Br J Ophthalmol*. 1994;78:24-29.
- Rassam SMB, Patel V, Kohner EM. The effect of acetazolamide

- on the retinal circulation. *Eye*. 1993;7:697-702.
- Rassam SMB, Patel V, Kohner EM. The effect of experimental hypertension on retinal vascular autoregulation in humans: a mechanism for the progression of diabetic retinopathy. *Exp Physiol*. 1995;80:53-68.
- Regillo CD, Sergott RC, Brown GC. Successful scleral buckling procedures decrease central retinal artery blood flow velocity. *Ophthalmology*. 1993;100:1044-1049.
- Rehkopf P, Friberg TR, Mandarino L, et al. Retinal circulation time using scanning laser ophthalmoscope-image processing techniques. In: Nasemann JE, Burk ROW, eds. *Scanning Laser Ophthalmoscopy and Tomography*. München: Quintessenz; 1990:81-89.
- Remulla J, Gaudio A, Miller S, Sandberg MA. Foveal electroretinograms and choroidal perfusion characteristics in fellow eyes of patients with unilateral neovascular age-related macular degeneration. *Br J Ophthalmol*. 1995;79:558-561.
- Richard GW. Differentiation of retinal circulation times by videoangiography. *Ophthalmologica*. 1985;191:161-163.
- Riehm E, Podesta HH, Bartsch C. Untersuchungen über die Durchblutung in Netzhautkapillaren bei intraokularen Drucksteigerungen. *Ophthalmologica*. 1972;164:249-254.
- Rimmer T, Fallon TJ, Kohner EM. Long-term follow-up of retinal blood flow in diabetes using the blue light entoptic phenomenon. *Br J Ophthalmol*. 1989;73:1-5.
- Riva CE, Ben-Sira I. A two-point fluorophotometer for the human ocular fundus. *Appl Opt*. 1975;14:2691-2693.
- Riva CE, Fekke GT, Ben-Sira I. Fluorescein dye-dilution technique and retinal circulation. *Am J Physiol*. 1978;234:H315-H322.
- Riva CE, Grunwald JE, Petrig BL. Autoregulation of human retinal blood flow. An investigation with laser Doppler velocimetry. *Invest Ophthalmol Vis Sci*. 1986;27:1706-1712.
- Riva CE, Grunwald JE, Sinclair SH. Laser Doppler measurement of relative blood velocity in the human optic nerve head. *Invest Ophthalmol Vis Sci*. 1982;22:241-248.
- Riva CE, Grunwald JE, Sinclair SH. Laser Doppler velocimetry study of the effect of pure oxygen breathing on retinal blood flow. *Invest Ophthalmol Vis Sci*. 1983;24:47-51.
- Riva CE, Grunwald JE, Sinclair SH, O'Keefe K. Fundus camera based retinal LDV. *Appl Opt*. 1981;20:117-120.
- Riva CE, Grunwald JE, Sinclair SH, Petrig BL. Blood velocity and volumetric flow rate in human retinal vessels. *Invest Ophthalmol Vis Sci*. 1985;26:1124-1132.
- Riva CE, Harino S, Petrig BL, Shonat RD. Laser Doppler flowmetry in the optic nerve. *Exp Eye Res*. 1992;55:499-506.
- Riva CE, Harino S, Shonat RD, Petrig BL. Circulation of the optic nerve head: an investigation with laser Doppler flowmetry. In: Drance SM, Van Buskirk EM, Neufeld AH, eds. *Pharmacology of Glaucoma*. Baltimore: Williams & Wilkins; 1992:253-264.
- Riva CE, Loeb M. Autoregulation of blood flow in the capillaries of the human macula. *Invest Ophthalmol Vis Sci*. 1977;16:568-571.
- Riva CE, Petrig B. Blue field entoptic phenomenon and blood velocity in the retinal capillaries. *J Opt Soc Am*. 1980;70:1234-1238.
- Riva CE, Petrig BO, Grunwald JE. Retinal blood flow. In: Shepherd AP, Öberg PA, eds. *Laser-Doppler Flowmetry*. Boston: Kluwer Academic Publishers; 1989:349-383.
- Riva CE, Pournaras CJ, Poitry-Yamate CL, Petrig BL. Rhythmic changes in velocity, volume, and flow of blood in the optic nerve head tissue. *Microvasc Res*. 1990;40:36-45.
- Riva CE, Shonat RD, Petrig BL, Pournaras CJ, Barnes JB. Noninvasive measurement of the optic nerve head circulation. In: Lambrou GN, Greve EL, eds. *Ocular Blood Flow in Glaucoma: Means, Methods, and Measurements*. Berkeley: Kugler & Ghedini; 1989:129-134.
- Riva CE, Shonat RD, Petrig BL, Pournaras CJ, Barnes JB. Non-invasive investigation of the optic nerve head circulation. In: *Noninvasive Assessment of the Visual System*, 1989 Technical Digest Series, vol 7. Washington, DC: Optical Society of America; 1989:158-161.
- Rivero ME, Bartsch DU, Otto T, Freeman WR. Automated scanning laser ophthalmoscope image montages of retinal diseases. *Ophthalmology*. 1999;106:2296-3000.
- Robinson F, Petrig BL, Riva CE. The acute effect of cigarette smoking on macular capillary blood flow in humans. *Invest Ophthalmol Vis Sci*. 1985;26:609-613.
- Robinson F, Riva C, Grunwald J, Petrig B, Sinclair S. Retinal blood flow autoregulation in response to an acute increase in blood pressure. *Invest Ophthalmol Vis Sci*. 1986;27:722-726.
- Roff EJ, Harris A, Chung HS, et al. Comprehensive assessment of retinal, choroidal and retrobulbar haemodynamics during blood gas perturbation. *Graefes Arch Clin Exp Ophthalmol*. 1999;37:984-990.
- Ross R, Barofsky J, Cohen G, Baber W, Palao S, Gitter K. Presumed macular choroidal watershed vascular filling, choroidal neovascularization, and systemic vascular disease in patients with age-related macular degeneration. *Am J Ophthalmol*. 1998;125:71-80.
- Rubanyi G, Polokoff M. Endothelins: molecular biology, biochemistry, pharmacology, physiology, and pathophysiology. *Pharmacol Rev*. 1994;46:325-415.
- Sakuri T, Yanagisawa M, Masaki T. Molecular characteristics of endothelin receptors. *Trends Pharmacol Sci*. 1992;13:103-108.
- Saracco JB, Gastaud P, Ridings B, Ubaud CA. The venous system of the peripheral choroid: I. The venous system of the pars plana. *Anat Clin*. 1983;5:177-185.
- Scheider A, Nasemann JE, Lund OE. Fluorescein and indocyanine green angiographies of central serous chorioidopathy by scanning laser ophthalmoscopy. *Am J Ophthalmol*. 1993;115:50-56.
- Schiodte SN, Scherfig E, Nissen OI. A pressure pulse amplitude lowering effect of retinal xenon photocoagulation in normotensive diabetic eyes. *Acta Ophthalmol (Copenh)*. 1981;59:170-178.
- Schmetterer L, Dallinger S, Findl O, Eichler HG, Wolzt M. A comparison between laser interferometric measurement of fundus pulsation and pneumotonometric measurement of pulsatile ocular blood flow: 1. Baseline considerations. *Eye*. 2000;14(pt 1):39-45.
- Schmetterer L, Dallinger S, Findl O, Graselli U, Eichler HG, Wolzt M. A comparison between laser interferometric measurement of fundus pulsation and pneumotonometric measurement of pulsatile ocular blood flow: 2. Effects of changes in pCO₂ and pO₂ and of isoproterenol. *Eye*. 2000;14(pt 1):46-52.
- Schmetterer L, Dallinger S, Findl O, et al. Noninvasive investigations of the normal ocular circulation in humans. *Invest Ophthalmol Vis Sci*. 1998;39:1210-1220.

- Schmetterer L, Findl O, Strenn K, et al. Ocular and systemic reactivity to isoprenaline in patients with insulin-dependent diabetes mellitus. *Eur J Clin Invest*. 1997;27:750-754.
- Schmetterer L, Wolzt M, Salomon A, et al. Effect of isoproterenol, phenylephrine, and sodium nitroprusside on fundus pulsations in healthy volunteers. *Br J Ophthalmol*. 1996;80:217-33.
- Schneider U, Inhoffen W, Gelissen F, Kreissig I. Assessment of visual function in choroidal neovascularization with scanning laser microperimetry and simultaneous indocyanine green angiography. *Graefes Arch Clin Exp Ophthalmol*. 1996;234:612-617.
- Schmetterer L, Lexer F, Unfried C, Sattmann H, Fercher A. Topical measurement of fundus pulsations. *Opt Eng*. 1995;34:711-716.
- Schulte K, Wolf S, Arend O, Harris A, Henle C, Reim M. Retinal hemodynamics during increased intraocular pressure. *German J Ophthalmol*. 1996;5:1-5.
- Seddon J, Ajani U, Sperduto RD, et al. Dietary carotenoids, vitamins A, C, and E, and advanced age-related macular degeneration. *JAMA*. 1994;272:1413-1420.
- Sergott RC, Abum NS, Trible JR, et al. Color Doppler Imaging: methodology and preliminary results in glaucoma. [Published erratum appears in *Surv Ophthalmol*. 1994;39:165] *Surv Ophthalmol*. 1994;38(suppl):S65-70.
- Sergott RC, Flaharty PM, Lieb WE, et al. Color Doppler imaging identifies four syndromes of the retrobulbar circulation in patients with amaurosis fugax and central retinal artery occlusions. *Trans Am Ophthalmol Soc*. 1992;90:383-402.
- Shimizu K. Sectorial order of fluorescein filling in the disc area. In: Shimizu K, ed. *Fluorescein Angiography*. Tokyo International Symposium, 1972; Tokyo: Igaku Shoin; 1974:349.
- Shin DH, Tsai CS, Parrow KA, Kim C, Wan JY, Shi DX. Intraocular pressure-dependent retinal vascular change in adult chronic open-angle glaucoma patients. *Ophthalmology*. 1992;98:1087-1092.
- Shiraki K, Moriwaki M, Yanagihara N, Kohno T, Miki T. Indocyanine green angiograms of choroidal nevi: comparison between confocal and nonconfocal scanning laser ophthalmoscope and fundus video camera. *Jpn J Ophthalmol*. 2001;45:368-374.
- Sieker HO, Hickam JB. Normal and impaired retinal vascular reactivity. *Circulation*. 1955;7:79-83.
- Sieker HO, Hickman JB, Gibson JF. The relationship between impaired retinal vasculature reactivity and renal function in patients with degenerative vascular disease. *Circulation*. 1955;12:64-68.
- Silver DM, Farrell RA, Langham ME, et al. Estimation of pulsatile ocular blood flow from intraocular pressure. *Acta Ophthalmologica Suppl*. 1989;191:25-29.
- Sinclair SH. Macular retinal capillary hemodynamics in diabetic patients. *Ophthalmology*. 1991;98:1580-1586.
- Sinclair SH, Azar-Cavanagh M, Soper KA, et al. Investigation of the source of the blue field entoptic phenomenon. *Invest Ophthalmol Vis Sci*. 1989;30:668-673.
- Sinclair SH, Grunwald JE, Riva CE, Braunstein SN, Nichols CW, Schwartz SS. Retinal vascular autoregulation in diabetes mellitus. *Ophthalmology*. 1982;89:748-750.
- Singh S, Dass R. The central retinal artery of the retina: 2. A study of its distribution and anastomoses. *Br J Ophthalmol*. 1960;44:280.
- Sloney DH, Freasier BD. Evaluation of optical radiation hazards. *Appl Optics* 1973;12:1-8.
- Smith R, Lee C, Charles HC, Farber M, Cunha-Vaz JG. Quantification of diabetic macular edema. *Arch Ophthalmol*. 1987;105:218-222.
- Sponsel WE, DePaul KL, Zetlan SR. Retinal hemodynamic effects of carbon dioxide, hyperoxia, and mild hypoxia. *Invest Ophthalmol Vis Sci*. 1992;33:1864-1869.
- Spraul CW, Lang GE, Ronzani M, Hogel J, Lang GK. Reproducibility of measurements with a new slit lamp-mounted ocular blood flow tonograph. *Graefes Arch Clin Exp Ophthalmol*. 1998;236:274-279.
- Squirrel DM, Watts A, Evans D, Mody C, Talbot JF. A prospective evaluation of the Heidelberg retina flowmeter in diagnosing ischaemia following branch retinal vein occlusion: a masked, controlled comparison with fluorescein angiography. *Eye*. 2001;15(pt 3):261-266.
- Steele EJ, Blunt MJ. The blood supply of the optic nerve and chiasma in man. *J Anat*. 1956;90:486.
- Stefansson E, Machemer R, de Juan E Jr, McCuen BW, Peterson J. Retinal oxygenation and laser treatment in patients with diabetic retinopathy. *Am J Ophthalmol*. 1992;113:36-38.
- Stodtmeister R, Hornberger M, Hofer M, et al. Ulrich and Ulrich oculo-oscillodermography: results in patients with healthy eyes. *Klinische Monatsblätter für Augenheilkunde*. 1988;192:219-233.
- Stone R, Laties A, Emson P. Neuropeptide Y and the ocular innervation of the rat, guinea pig, cat, and monkey. *Neuroscience*. 1986;17:1207-1216.
- Sugiyama K, Bacon DR, Morrison JC, Van Buskirk EM. Optic nerve head microvasculature of the rabbit eye. *Invest Ophthalmol Vis Sci*. 1992;33:2251-2261.
- Sugiyama K, Bacon DR, Morrison JC, Van Buskirk EM. The effect of phenylephrine on the ciliary body and optic nerve head vasculature. *J Glaucoma*. 1992;1:156.
- Tacke CM, Schradin T, Lang GE, et al. Ocular blood flow in insulin dependent diabetic patients. ARVO Abstract. *Invest Ophthalmol Vis Sci*. 1994;35(suppl):1594.
- Takagi C, King GL, Takagi H, et al. Endothelin-1 action via endothelin receptors is a primary mechanism modulating retinal circulatory response to hyperoxia. *Invest Ophthalmol Vis Sci*. 1996;37:2099-2109.
- Takahashi K, Brooks RA, Kanse SM, et al. Production of endothelin 1 by cultured bovine retinal endothelial cells and presence of endothelin receptors on associated pericytes. *Diabetes*. 1989;38:1200-1202.
- Tamaki Y, Araie M, Kawamoto E, Eguchi S, Fujii H. Noncontact, two-dimensional measurement of retinal microcirculation using laser speckle phenomenon. *Invest Ophthalmol Vis Sci*. 1994;35:3825-3834.
- Tamaki Y, Nagahara M, Yamashita H, Kikuchi M. Analysis of blood flow velocity in the ophthalmic artery by color Doppler imaging: 1. Studies on normal human eyes. *J Jpn Ophthalmol Soc*. 1993;97:175-180.
- Tamaki Y, Nagahara M, Yamashita H, Kikuchi M. Analysis of blood flow velocity in the ophthalmic artery by color Doppler imaging: 2. Studies on diabetic eyes. *J Jpn Ophthalmol Soc*. 1993;97:961-966.

- Tamaki Y, Nagahara M, Yamashita H, Kikuchi M. Blood velocity in the ophthalmic artery determined by color Doppler imaging in normal subjects and diabetics. *Jpn J Ophthalmol*. 1993;37:385-392.
- Tanaka T, Muraoka K, Shimizu K. Fluorescein fundus angiography with scanning laser ophthalmoscope: visibility of leukocytes and platelets in perifoveal capillaries. *Ophthalmology*. 1991;98:1824-1829.
- Taylor KJW, Holland S. Doppler US: Part I. Basic principles, instrumentation, and pitfalls. *Radiology*. 1990;174:297-307.
- Trew DR, Smith SE. Postural studies in pulsatile ocular blood flow: II. Chronic open angle glaucoma. *Br J Ophthalmol*. 1991;75:71-75.
- Tribble JR, Sergott RC, Spaeth GL, et al. Trabeculectomy is associated with retrobulbar hemodynamic changes. *Ophthalmology*. 1994;101:340-351.
- Tsukahara H, Gordienko D, Tonshoff B, Gelato M, Goligorsky M. Direct demonstration of insulin-like growth factor-I-induced nitric oxide production by endothelial cells. *Kidney Int*. 1994;45:598-604.
- Ulrich W-D, Ulrich CH. Oculo-oscillo-dynamography: a diagnostic procedure for recording ocular pulses and measuring retinal and ciliary arterial blood pressures. *Ophthalmic Res*. 1985;17:308-317.
- Ulrich W-D, Ulrich C, Walther G. Ocular perfusion pressure and oculo-oscillo-dynamography. In: Lambrou GN, Greve EL, eds. *Ocular Blood Flow in Glaucoma*. Berkeley: Kugler & Ghedini; 1989:101-114.
- Van Assendelft OW. *Spectrophotometry of Haemoglobin Derivatives*. 1970, Charles C. Thomas; Assen, The Netherlands: Royal Vangorcum Ltd.
- Vane JR, Anggard EE, Botting R. Regulatory function of the vascular endothelium. *N Engl J Med*. 1990;323:27-36.
- Von Bibra H, Stempfle HU, Poll A, et al. [Accuracy of various Doppler techniques in recording blood flow velocity. Studies in vitro.] *Z Kardiol*. 1990;79:73-82.
- Von Helmholtz H. Beschreibung eines Augen-Spiegels zur Untersuchung der Netzhaut im lebenden Auge. Berlin, A. Forstner, 1851 (Description of an ophthalmoscope for examining the retina of the living eye. Hollenhorst RW trans). *Arch Ophthalmol*. 1951;46:565-583.
- Ward JB, Hedges TR 3rd, Heggerick PA. Reversible abnormalities in the ophthalmic arteries detected by ocular Doppler imaging. *Ophthalmology*. 1995;102:1606-1610.
- Watkins R, Beigi B, Yates M, Chang B, Linardos E. Intraocular pressure and pulsatile ocular blood flow after retrobulbar and peribulbar anaesthesia. *Br J Ophthalmol*. 2001;85:796-798.
- Webb RH, Hughes GW, Delori FC. Confocal scanning laser ophthalmoscope. *Appl Opt*. 1987;26:1492-1499.
- Webb RH, Hughes GW, Pomerantzeff O. Flying spot TV ophthalmoscope. *Appl Opt*. 1980;19:2991-2997.
- Weigelin E, Lestein A. *Ophthalmodynamometry*. New York: Hafner; 1963.
- Weinreb RB. Why study the ocular microcirculation in glaucoma? *J Glaucoma*. 1992;1:145-147.
- Wenzel R, Noll G, Luscher T. Endothelin receptor antagonists inhibit endothelin in human skin microcirculation. *Hypertension*. 1994;23:581-586.
- West S, Rosenthal E, Bressler NM, et al. Exposure to sunlight and other risk factors for age-related macular degeneration [see comments]. *Arch Ophthalmol*. 1989;107:875-879.
- Williamson TH. What is the use of ocular blood flow measurement? *Br J Ophthalmol*. 1994;78:326.
- Williamson T, Baxter G. Central retinal vein occlusion, an investigation by color Doppler imaging: blood velocity characteristics and prediction of iris neovascularization. *Ophthalmology*. 1994;101:1362-1372.
- Williamson TH, Baxter GM, Dutton GN. Colour Doppler velocimetry of the arterial vasculature of the optic nerve head and orbit. *Eye*. 1993;7:74-79.
- Williamson TH, Harris A. Color Doppler ultrasound of the eye and orbit. *Surv Ophthalmol*. 1996;40:225-267.
- Williamson TH, Harris A, Martin BJ. Reproducibility of color Doppler imaging assessment of blood flow velocity in orbital vessels. *J Glaucoma*. 1995;4:281-286.
- Wolf S, Arend O, Jung E, et al. Mikrostrombahn und mikro-zirkulation im perimakulären Kapillarnetz. *Ophthalmologie*. 1992;89:45-49.
- Wolf S, Arend O, Reim M. Measurement of retinal hemodynamics with scanning laser ophthalmoscopy: reference values and variation. *Surv Ophthalmol*. 1994;38(suppl): S95-S100.
- Wolf S, Arend O, Sponkel WE, et al. Retinal hemodynamics using scanning laser ophthalmoscopy and hemorheology in chronic open-angle glaucoma. *Ophthalmology*. 1993;100:1561-1566.
- Wolf S, Arend O, Toonen H, et al. Measurement of retinal micro- and macrocirculation in patients with diabetes mellitus with scanning laser ophthalmoscopy. *Clin Vision Sci*. 1992;7:461-469.
- Wolf S, Arend O, Toonen H, et al. Retinal capillary blood flow measurement with a scanning laser ophthalmoscope: preliminary results. *Ophthalmology*. 1991;98:996-1000.
- Wolf S, Jung E, Keisewetter H, Körber N, Reim M. Video fluorescein angiography: method and clinical application. *Graefes Arch Clin Exp Ophthalmol*. 1989;227:145-151.
- Wolf S, Toonen H, Arend O, et al. Zur Quantifizierung der retinalen Kapillardurchblutung mit Hilfe des Scanning-Laser-Ophthalmoskops. *Biomed Tech*. 1990;35:131-134.
- Wolf S, Toonen H, Koyama T, Meyer-Ebrecht D, Reim M. Scanning laser ophthalmoscopy for the quantification of retinal blood-flow parameters: a new imaging technique. In: Nasemann JE, Burk ROW, eds. *Scanning Laser Ophthalmoscopy and Tomography*. München: Quintessenz; 1990:91-96.
- Wood EH. Definitions and symbols for terms commonly used in relation to indicator dilution curves. *American Heart Association Monograph #4*. Symposium on use of indicator dilution techniques. 1962;10:(3; pt 2):379-380.
- Wu DC, Schwartz B, Schworer J, et al. Retinal blood vessel width measured on color fundus photographs by image analysis. *Acta Ophthalmol Scand*. 1995;73(suppl 215):33-40.
- Wybar KC. Anastomoses between the retina and ciliary arterial circulations. *Br J Ophthalmol*. 1956;40:65.
- Yamamoto T, Kitazawa Y. Vascular pathogenesis of normal-tension glaucoma: a possible pathogenetic factor, other than intraocular pressure, of glaucomatous optic neuropathy. *Prog Retin Eye Res*. 1998;17:127-143. Review.
- Yamazaki S, Baba H, Tokoro T. Effects of timolol and carteolol on ocular pulsatile blood flow. *Acta Soc Ophthalmol Jpn*. 1992;96:973-977.

- Yaoeda K, Shirakashi M, Funaki S, Funaki H, Nakatsue T, Abe H. Measurement of microcirculation in the optic nerve head by laser speckle flowgraphy and scanning laser Doppler flowmetry. *Am J Ophthalmol*. 2000;129:734-739.
- Yaoeda K, Shirakashi M, Funaki S, et al. Measurement of microcirculation in optic nerve head by laser speckle flowgraphy in normal volunteers. *Am J Ophthalmol*. 2000;130:606-610.
- Yap MKH, Brown B. The repeatability of the noninvasive blue field entoptic phenomenon method for measuring macular capillary blood flow. *Opt Vis Sci*. 1994;71:346-349.
- Yoshida A, Fekke GT, Green G, et al. Retinal circulatory changes after scleral buckling procedures. *Am J Ophthalmol*. 1983;95:182-188.
- Yoshida A, Fekke GT, Morales-Stopello J, Collas GD, Goger DG, McMeel JW. Retinal blood flow alterations during progression of diabetic retinopathy. *Arch Ophthalmol*. 1983;101:225-227.
- Yoshida A, Fekke GT, Ogasawara H, et al. Effect of timolol on human retinal, choroidal, and optic nerve head circulation. *Ophthalmic Res*. 1991;23:162-170.
- Yoshida A, Ogasawara H, Fujio N, et al. Comparison of short and long-term effects of betaxolol and timolol on human circulation. *Eye*. 1998;12:848-853.
- Yoshida A, Ogasawara H, Konno S. Reproducibility and applications of a newly developed stabilized laser Doppler velocimetry system [ARVO abstract]. *Invest Ophthalmol Vis Sci*. 1997;38:S775. Abstract 3588.
- Young R. Pathophysiology of age-related macular degeneration. *Surv Ophthalmol*. 1987;31:291-306.
- Yung CW, Harris A, Massicotte S, et al. Retinal blood flow indices in patients infected with human immunodeficiency virus. *Br J Ophthalmol*. 1996;80:723-727.
- Yung C, Harris A, Massicotte S, et al. Retinal blood flow indices in patients infected with human immunodeficiency virus. *Br J Ophthalmol*. 1996;80:723-727.
- Zeimer R, Guran T, Shahidi M, Mori M. Application of targeted dye delivery to the mapping of retinal hemodynamics. In: *Digest of Topical Meeting on Noninvasive Assessment of the Visual System*, 1990, Vol 3. Washington DC: Optical Society of America; 1990:84-87.
- Zhao J, Frambach D, Lee P, Lee M, Lopez P. Delayed macular choriocapillary circulation in age-related macular degeneration. *Int Ophthalmol*. 1995;19:1-12.
- Zinn IG: *Descriptio anatomica oculi humani*. 1st ed. Gottigen: Abrami Vandenhoeck; 1755:216.

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Atlas of Ocular Blood Flow

Vascular Anatomy, Pathophysiology, and Metabolism

*Alon Harris, MSc, PhD • Christian P. Jonescu-Cuypers, MD, PhD
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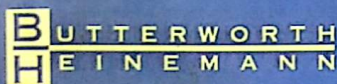
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