

Chapter 2

Pathophysiology of Retinal Vein Occlusions

The pathophysiology of retinal vein occlusion (RVO) consists of the three components of Virchow's triad – abnormalities of the vessel wall (considered in Chap. 1), alterations in the blood (e.g., abnormalities of viscosity and coagulation), and alterations in blood flow.¹ This chapter addresses alterations of the blood and of blood flow.

This chapter begins with thrombosis, the cause of the venous occlusion, followed by retinal hemodynamics, the driving force for transudation, including a review of vascular autoregulation. Then it covers pathophysiologic processes that result from venous occlusions including macular edema, serous retinal detachment, and intraocular neovascularization. The underlying processes include:

- Oxygenation of the retina
- Regulation of the blood–retina barrier
- Active transport across the retinal pigment epithelium
- Biochemical pathways involved in angiogenesis
- Glial–vessel interactions
- Intrinsic functions of retinal endothelial cells and pericytes such as contractility, antioxidation, and antithrombosis²

Coverage of physiologic concepts relevant to RVO involves formulas, biochemical pathways, and conceptual block diagrams involving abbreviations. Within the text, each abbreviation will be introduced at the first occurrence of the term it represents. For ease of reference, these abbreviations are listed in Table 2.1.

2.1 Abnormalities of the Blood

2.1.1 Thrombosis

Thrombosis and thrombolysis are involved in every RVO, so an understanding of these biochemical pathways is important. Paradoxically, predisposition to thrombosis, thrombophilia, has the least impact of the three components of Virchow's triad from a public health perspective (abnormalities of the vessel wall have the most).³ Nevertheless, thrombophilia plays a role in a few RVOs, and familiarity with genetic and acquired maladies of coagulation and fibrinolysis has a role in clinical care of some patients.

Thrombosis can be considered to be the result of an imbalance of opposing pathways – coagulation (Fig. 2.1 and Table 2.2) and fibrinolysis (Fig. 2.2). A common pathway leading to thrombosis in all forms of RVO can be outlined as follows. Retinal venous endothelium becomes damaged from turbulent blood flow induced by an adjacent sclerotic arteriole. This exposes types I and III collagen fibrils to the lumen where they bind to platelet receptors. The most important ligand for platelet adhesion receptors is von Willebrand factor (VWF) a glycoprotein present in blood plasma and produced by endothelium, megakaryocytes, and subendothelial connective tissue. VWF links the exposed collagen to platelet glycoprotein (GP) receptor Ib (GPIb) and binds factor VIII which promotes further platelet

Table 2.1 Abbreviations used in pathophysiology of retinal vein occlusions

Abbreviation	Term
ACE	Angiotensin-converting enzyme
AT	Antithrombin
AU	Arbitrary units
bFGF	Basic fibroblast growth factor
BAB	Blood–aqueous barrier
BRB	Blood–retina barrier
Q	Blood flow in volume per second
BRVO	Branch retinal vein occlusion
CRA	Central retinal artery
CRV	Central retinal vein
CRVO	Central retinal vein occlusion
DBP	Diastolic blood pressure
EGF	Epidermal growth factor
EPO	Erythropoietin
GP	Glycoprotein
HIF	Hypoxia-inducible factor
IGF	Insulin-like growth factor
ICAM-1	Intercellular adhesion molecule-1
IP-10	Interferon-gamma-inducible 10-kD protein
IL	Interleukin
IOP	Intraocular pressure
MIP	Macrophage-inhibitory protein
P_a	Mean arterial pressure
MCP	Monocyte chemotactic protein
MIG	Monokine induced by interferon gamma
NVI	Neovascularization of the iris
NO	Nitric oxide
NF- $\kappa\beta$	Nuclear factor-kappa β
OPP	Ocular perfusion pressure
PRP	Panretinal photocoagulation
pO_2 , pCO_2	Partial pressure of oxygen, carbon dioxide
PTT	Partial thromboplastin time
PEGF	Pigment epithelial derived growth factor
PGF	Placental growth factor
PAI	Plasminogen activator inhibitor
PDGF	Platelet derived growth factor
PCA	Posterior ciliary artery
ΔP	Pressure drop along a length of vessel
PT	Prothrombin time
PG	Prostaglandins
RAS	Renin angiotensin system
RPE	Retinal pigment epithelium
RVO	Retinal vein occlusion
P_v	Retinal venous pressure
RNA	Ribonucleic acid
SVP	Spontaneous venous pulsations
SBP	Systolic blood pressure
ZO-1	Tight junction protein

Table 2.1 (continued)

TPA	Tissue plasminogen activator
TGF	Transforming growth factor
P	Transmural pressure for the vessel wall
TNF	Tumor necrosis factor
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
VOP	Venous outflow pressure
L	Vessel length
R	Vessel radius
T	Vessel wall tension
η	Viscosity of the blood
VWF	Von Willebrand Factor

adhesion to the endothelium.^{5,6} Therefore, higher than normal levels of VWF are prothrombotic. Thrombospondin that is stored in platelets is released upon platelet adhesion and subsequent activation, overcoming the antithrombotic effects of nitric oxide and boosting further adhesion of platelets to the damaged vessel wall. Other ligands that attach to platelet receptors and mediate platelet clumping at endothelial wounds include laminin, fibronectin, vitronectin, and fibrinogen. There are many other platelet adhesion receptors besides GPIb. Their relative importance and roles are being studied.⁶⁻⁸

Once platelets adhere to a damaged venous wall, they bind others into a growing nidus. Platelet-to-platelet adhesion is mediated by GPIIb/GPIIIa receptors that are normally hidden, but are exposed for binding by platelet activation. Adenosine diphosphate, epinephrine, thrombin, and adhesion of the platelet to collagen lead to exposure of the GPIIb/GPIIIa receptors. This happens either indirectly via a pathway mediated by arachidonic acid release or directly if the arachidonic acid pathway is blocked.⁸ Fibronectin stored in platelets is released during platelet activation and further mediates platelet–platelet adhesion.⁶

The negatively charged platelet surface provides a platform for assembly of activated coagulation factors that results in thrombin generation.⁶ Selectins are cellular adhesion molecules released during platelet activation that are important in this process, promoting fibrin formation.⁶ A myriad of

further mediators of platelet–vascular wall interaction exist with a complicated mesh of feedback pathways that tip the scale toward or away from thrombosis.⁶

The clotting cascade that is triggered on the platform of the platelet nidus is a series of biochemical reactions resulting in the production of fibrin from circulating fibrinogen (Fig. 2.1). Most of the enzymes in the clotting cascade are serine proteases, but factors V, VIII, and XII are glycoproteins, and factor XIII is a transglutaminase.⁹ Clotting factors circulate as inactive precursors called zymogens.

There are two aspects of the clotting cascade, the extrinsic (or tissue-factor) system and the intrinsic (or contact-activation) system. The extrinsic system activates coagulation more often than the intrinsic system (Fig. 2.1). The extrinsic pathway begins when blood vessel damage activates factor VII through the mediation of tissue factor that is expressed by fibroblasts and leukocytes. The concentration of factor VII in the blood is the highest of all coagulation factors. Once factor VII is activated to factor VIIa, the other reactions in the extrinsic pathway follow, beginning with the activation of factor IX and X.³

In the intrinsic pathway, a stimulus such as exposure of subendothelial collagen promotes formation of a complex of high molecular weight kininogen, prekallikrein, and factor XII. Factor XII is activated and the reactions of the intrinsic pathway follow. The extrinsic and intrinsic pathways both lead to a final common pathway involving factor X, thrombin, and fibrin.³ Thrombin converts fibrinogen into fibrin monomers and indirectly serves to cross-link the fresh fibrin thrombus, trapping erythrocytes, leukocytes, and platelets.^{10,11}

The final common coagulation pathway is subject to negative feedback in many ways. It is checked by antithrombin (AT), protein C, protein S, tissue factor pathway inhibitor, and heparin cofactor II. Deficiencies of any of these factors are prothrombotic.³ Antithrombin is an α_2 -glycoprotein that is the main inhibitor of thrombin. Heparin potentiates its inhibition of thrombin, hence its synonym heparin cofactor.^{12,13} Once a

clot has formed and covers damaged endothelium, it extends until it reaches normal endothelium where it interacts with thrombomodulin, a protein that binds thrombin and inactivates it. The thrombomodulin–thrombin complex activates protein C which in turn degrades procoagulant factors Va and VIIIa retarding coagulation.^{4,14} A genetic mutation in the factor V gene produces a resistance to the effect of activated protein C and leads to thrombophilia.^{4,14,15}

Of equal importance to the coagulation cascade is the pathway for thrombolysis which balances coagulation (Fig. 2.2). Plasminogen is a zymogen released by the liver and activated to plasmin by several enzymes including tissue plasminogen activator, urokinase plasminogen activator, kallikrein, and factor XII. Plasmin degrades fibrin, so a plasminogen deficiency is prothrombotic. Tissue plasminogen activator (TPA) is secreted by vascular endothelium and promotes the proteolysis of fibrin in the presence of plasminogen. Exercise, venous occlusion, epinephrine, nicotinic acid, desmopressin acetate, and ethanol increase the basal concentration of TPA.¹⁶ The complexity of the pathways is illustrated by the presence of inhibitors of TPA including alpha 2 plasmin inhibitor, plasminogen activator inhibitor (PAI)-1, and PAI-2. Elevation in all of these are prothrombotic influences. Thrombolysis depends on thrombus age with increasing age conferring resistance to lysis.¹⁶ In clinical practice, patients are often excluded for consideration of attempts at thrombolysis if they are seen too long after onset of symptoms (e.g., >72 h).¹⁷

The coagulation and fibrinolysis systems form a basis for understanding thrombosis, but there are ancillary systems that add to the complexity. For example, antiphospholipid antibodies promote thrombosis. They are directed against phospholipids on vascular endothelial and platelet membranes increasing the likelihood of platelet adherence to the vessel wall. Some of them impair the anticoagulant activity of activated protein C, reducing fibrinolysis, and dysregulate the balance of the prostacyclin–thromboxane system, increasing levels of VWF, impairing activity of thrombomodulin, and activating platelet aggregation.¹⁸

Others bind to prothrombin, factor Xa, and protein S promoting coagulation.¹⁹

In clinical care, the performance of the intrinsic system is measured by the partial thromboplastin time (PTT) and the performance of the extrinsic system by the prothrombin time (PT).³ Thrombin–antithrombin complex is an indirect indicator of a systemically activated coagulation system and can be clinically useful. Higher values indicate an increase in thrombin generation, a reflection of a procoagulant diathesis.²⁰

A straightforward understanding of the clotting pathway does not translate directly into clinical insight. For example, intuition suggests that a deficiency of factor VII would predispose to a bleeding disorder, but paradoxically, a genetic deficiency of factor VII is thrombophilic.⁹ Some factors, such as factor XII, are involved in both the coagulation pathway and the fibrinolysis pathway. Nevertheless, a deficiency of factor XII overall is prothrombotic.²¹ When antiheparin antibodies develop after heparin therapy, the induced thrombocytopenia does not lead to increased bleeding as intuition would suggest, but rather to thrombosis, presumably because the antiheparin–platelet antibody also activates the clotting cascade.²² Finally, thrombosis is a critical part of the pathophysiology of RVO, but there are many cases of RVO developing in patients taking warfarin, aspirin, other platelet-aggregation inhibitors, and combinations of various anticoagulant drugs.^{23–25}

Beyond the acute stage of thrombosis, slower changes continue to occur. From 7 to 14 days after acute thrombosis, fibroblasts, endothelial cells, and inflammatory cells invade the clot. From 3 to 8 months recanalization of the clot occurs.^{10,26}

2.1.2 Viscosity of Blood

Generally, viscosity is the resistance to flow of a fluid caused by friction between adjacent layers of the fluid. A precise definition is the ratio of the applied force (shear stress) to the differential

velocity of two layers of fluid (shear rate). For simple, or Newtonian, fluids such as water and plasma, the rate of flow under nonturbulent conditions is directly proportional to the applied force. Viscosity depends on temperature, increasing as the temperature decreases. Newtonian fluids are assigned a relative viscosity defined as their viscosity divided by the viscosity of water at the same temperature. Plasma at 37°C has a relative viscosity of 1.8.

For complicated, or non-Newtonian, fluids such as blood, the relationship of shear force to differential velocity of the fluid layers is dependent on the shear rate as a result of molecular interactions among the cellular components, electrolytes, and proteins. A lower shear rate increases viscosity. The main determinants of blood viscosity are hematocrit and plasma fibrinogen. The greater the number of red cells per unit volume, the larger the aggregates of red cells. Fibrinogen is the linking molecule in the red cell aggregates.²⁷ Blood viscosity increases exponentially as the hematocrit increases (Fig. 2.3).²⁹ Greater rigidity of erythrocytes, as in local acidosis or sickling, also increases viscosity.²⁷ Other variables including age, time of day, and posture influence blood viscosity in less well-defined ways.³⁰

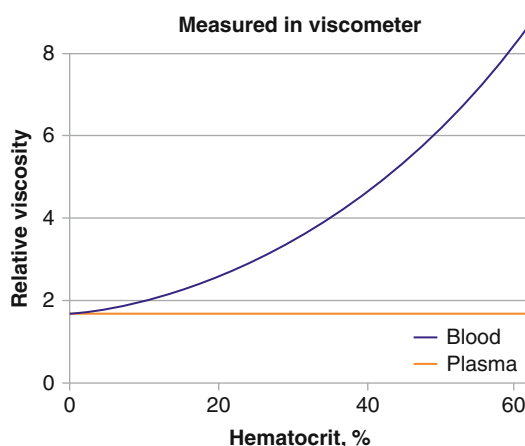


Fig. 2.3 Graph of the dependence of relative viscosity of blood on hematocrit (Redrawn from Whittaker and Winton²⁸)

In vivo, as blood enters capillaries, there is an effective reduction in hematocrit as the red cells move to the center of the lumen and plasma lines the walls, a phenomenon termed the Fahraeus–Lindqvist effect. The reduced hematocrit lowers blood viscosity, an effect that more than offsets the increased blood viscosity resulting from the lower shear rate of blood within the capillaries. The net effect is that blood viscosity in capillaries is lower than that measured in vitro with a viscometer.

Because the retinal venous circulation is characterized by low flow and high vascular resistance, it is particularly affected by blood viscosity.³¹ Erythrocyte aggregation is the main determinant of blood viscosity at low flow rates and has been found to be elevated in CRVO in some, but not all, studies.³¹ Stagnation of blood flow may predispose to thrombosis in the genesis of RVO and may worsen ischemia once RVO has occurred.^{32,33} As clotting begins, the molecular interactions of the proteins and cellular components of the blood change, and the viscosity dramatically increases. Interventions for RVO that reduce hematocrit such as isovolemic hemodilution reduce the viscosity of the blood and increase retinal blood flow velocity.³²

2.2 Abnormalities of Blood Flow

2.2.1 Retinal Vascular Hemodynamics

The driving pressure for blood flow through the retinal vasculature is the ocular perfusion pressure, defined as:

$$OPP = (DBP + [SBP - DBP] / 3) - P_v,$$

where

OPP=ocular perfusion pressure

DBP=diastolic blood pressure

SBP=systolic blood pressure

P_v =intravascular pressure in the major retinal veins

The term in parentheses is defined as the mean arterial pressure, P_a . P_v normally approximates the intraocular pressure (IOP), thus under normal conditions:

$$OPP = P_a - IOP^{32,33}$$

In actuality, P_v must be slightly greater than IOP for the retinal veins to remain patent. However, the transmural difference in pressure is small, so the approximation is reasonable. Some have suggested that primary open-angle glaucoma predisposes an eye to CRVO because it reduces the OPP as can be seen from the equation.³⁴

The uveal venous pressure cannot be measured directly in humans and is difficult to measure in animals, but logic suggests a lower bound. As long as blood flows through the uveal veins, the uveal venous pressure must be slightly higher than the IOP. By indirect measurement methods in rabbits and imperfect direct measurements in cats, it has been concluded that the uveal venous pressure is approximately 1 mmHg higher than the intraocular pressure at normal and high IOP.³⁵ At high IOP, the partial collapse of the uveal veins increases their resistance and allows their pressure to rise and maintain a slight elevation relative to IOP to maintain their patency.

Hemodynamic principles imply that the intravascular pressure is lowest in the venae cavae as they join the heart and increases toward the venous periphery. The same principle applies within the eye: the retinal venous pressure is lowest where the hemicentral retinal veins join to form the central vein and increases toward the periphery of the retinal venous tree. In the choroid, the intravenous pressure is higher in the postcapillary venules than in the vortex veins.³⁶ Although we cannot directly measure intravascular pressure within many parts of the ocular vascular tree, these hemodynamic principles together with measurements that we can make in the carotid artery and vena cava allow us to construct a diagram with hypothetical, but reasonable, estimates of intravascular pressures at different

points within the ocular and orbital vascular tree (Fig. 2.4).

Figure 2.4a diagrams the anatomic structures involved, and Fig. 2.4b simplifies the situation to a block diagram showing connections and intra-vascular pressures at important locations within

the circuit. Of course, pressure declines continuously in traversing the circuit, not in steps, as is sketched. For heuristic purposes, the diagram makes explicit assumptions about intraluminal pressures at various points in the vascular circuit where actual measurements are lacking.

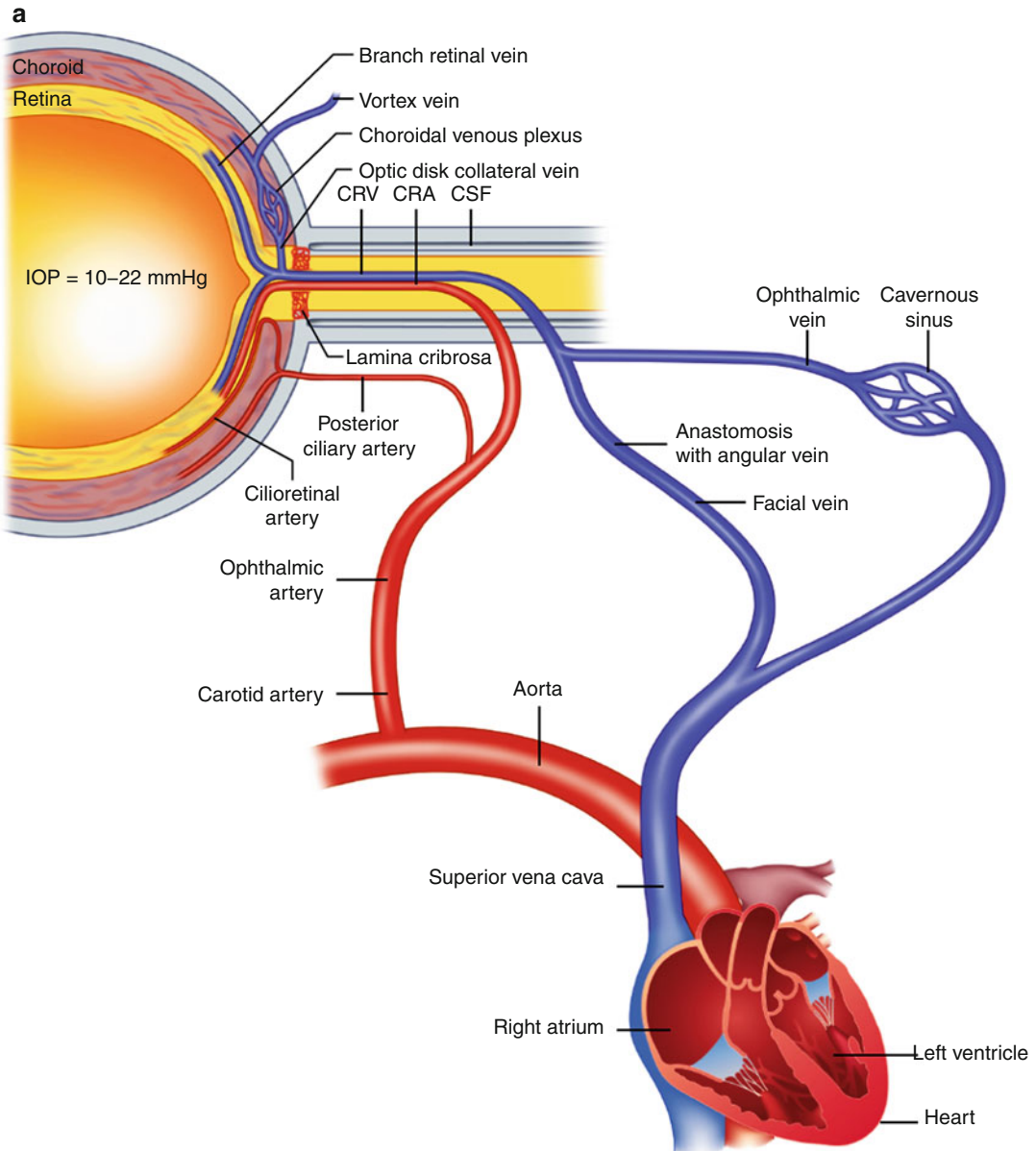


Fig. 2.4 (a) Diagram of the connections and circuits important in determining central retinal venous physiology and hemodynamics. (b) Block diagram of A with

measured intraluminal pressures where possible and assumptions where no measurements exist

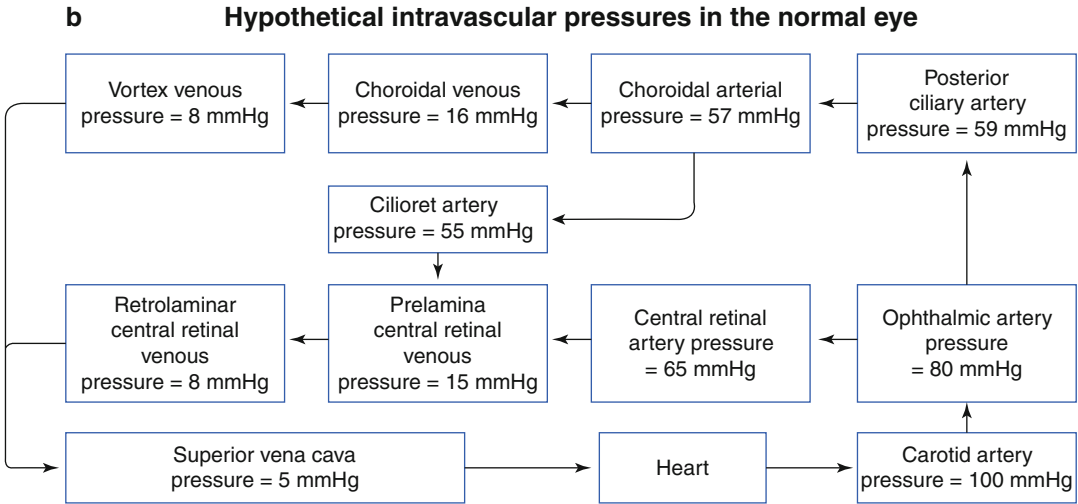


Fig. 2.4 (continued)

2.2.1.1 Laplace's Law

Laplace's law for thin-walled cylindrical vessels states that:

$$T = P \cdot R$$

where

T = vessel wall tension

P = transmural pressure for the vessel wall

R = vessel radius (Fig. 2.5)

A vessel is thin walled if the vessel radius is greater than five times the wall thickness, a condition met by retinal vessels. As an everyday example of Laplace's law, the wall tension of a balloon increases as the radius of the balloon increases while blowing it up. Laplace's law is useful in estimating quantities such as capillary intraluminal pressure that are impossible to measure with current techniques. For example, the radius of choroidal capillaries is larger than the radius of retinal capillaries, but the capillary walls are not thicker. Similar wall morphology and thickness suggest that an assumption of equal wall tension of choroidal and retinal capillaries is reasonable. Laplace's law implies, therefore, that the intraluminal pressure in a choroidal capillary should be greater than that in a retinal capillary, although we are unable to measure either quantity.³⁷

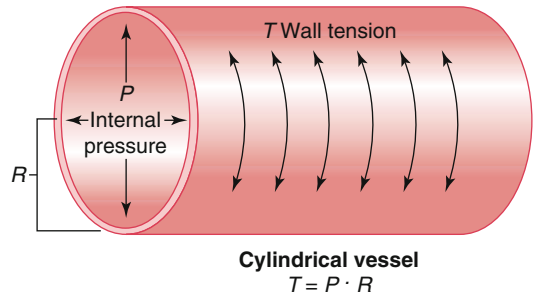


Fig. 2.5 Diagram illustrating Laplace's law for a thin-walled cylindrical tube such as a retinal vein. R radius of the tube, P intraluminal pressure, T wall tension

Experimental evidence to the contrary is also interpreted using Laplace's law. Blumenthal and colleagues did experiments showing that the retinal circulation ceases at an intraocular pressure greater than that at which the choroidal circulation ceases which is in turn higher than that at which the optic disc circulation ceases.³⁷ They raised intraocular pressure in human subjects using a scleral suction cup until the central retinal artery, choroidal, and optic disc circulations stopped. They then injected fluorescein dye into each subject's brachial vein and slowly lowered intraocular pressure while recording the IOP at which dye appeared in the retinal, choroidal, and

optic disc capillaries. They assumed that the resistance to blood flow in all three vascular beds – retina, choroid, and optic disc – was primarily determined by the capillaries.

Retinal vessels began to fill when the IOP dropped below systolic pressure, the critical transmural pressure, $P_{\text{critical transmural}}$. Choroidal capillaries filled when the intraocular pressure fell further – when the IOP was 7 mmHg less than SBP. A typical value for the critical closing value for the choroidal circulation was approximately 70 mmHg.¹ The intraocular pressure had to fall further, to approximately 60 mmHg, before the optic disc capillaries began to fill. The applicable form of Laplace's law in this experiment is $P_{\text{critical transmural}} = T / R$. Histologic studies have shown that R for choroidal capillaries is greater than for retinal and optic disc capillaries. Based on similar capillary wall morphology and thickness, the authors initially assumed that T was likely to be equal for choroidal and retinal capillaries. Laplace's law would, therefore, imply that for the same T , $P_{\text{critical transmural}}$ should be lower for the choroidal circulation. Yet the results of the experiments were consistently the reverse: $P_{\text{critical transmural}}$ was higher for the choroidal than the retinal capillaries. From this counterintuitive observation, it was deduced that the tension in the wall of a choroidal capillary was higher than in the wall of a retinal capillary. The authors named this incremental capillary wall tension the vascular tone and concluded that it must be higher in the choroid than the retina or optic disc.³⁷

2.2.1.2 Poiseuille's Law

Poiseuille's law expresses how intraluminal pressure varies for a fluid traveling down a cylindrical tube. It states that the pressure drop over a

segment of a vessel increases if the vessel radius decreases or the segment length increases and that the dependence on radius is far stronger than that on segment length. Mathematically,

$$\Delta P = 8Q\eta L / R^4,$$

where

ΔP = change in intravascular pressure over the length of a vessel

Q = blood flow in volume per second

η = blood viscosity

L = vessel length

R = vessel radius

Thus, when a retinal arteriole dilates, the pressure drops less over the length of the arteriole, leading to an increase in intravascular pressure at the downstream capillaries.

Poiseuille's law is significant in many clinical contexts. Consider, for example, the implications of arteriolar constriction to an affected sector of retina in BRVO after grid laser.^{38,39} Reduction in arteriolar radius implies that the intravascular pressure transmitted to the retinal capillaries is decreased. Due to the fourth power dependence of the intravascular pressure gradient on vessel radius, even small changes in radius are associated with large decreases in retinal capillary pressure.⁴⁰

Poiseuille's law is also applicable when considering the effects of elevated vascular endothelial growth factor (VEGF) on retinal capillary luminal diameter. VEGF causes capillary luminal diameter to decrease as a result of endothelial cell hypertrophy. According to Poiseuille's law, this decreases the blood flow across the retinal capillary – assuming that the ocular perfusion pressure has not changed – exacerbating the ischemia and promoting a further increase in tissue hypoxia and VEGF upregulation. A vicious cycle resulting in retinal capillary nonperfusion could be the outcome, and indeed, conversion of less ischemic to more ischemic RVO has been observed.⁴¹

A third application of Poiseuille's law is in interpreting the retinal vascular response to hyperviscosity (Fig. 2.6).⁴² Under conditions of hyperviscosity, retinal blood flow decreases, and

¹The astute reader will question how a typical critical closing value can be approximately 70 mmHg and yet approximately 7 mmHg less than SBP. SBP is usually quite a bit higher than 77 mmHg. The only thing I can think of is that the scleral suction cup gave the experimental subjects a bit of a vagal reaction. In any case, those numbers are what the paper states.

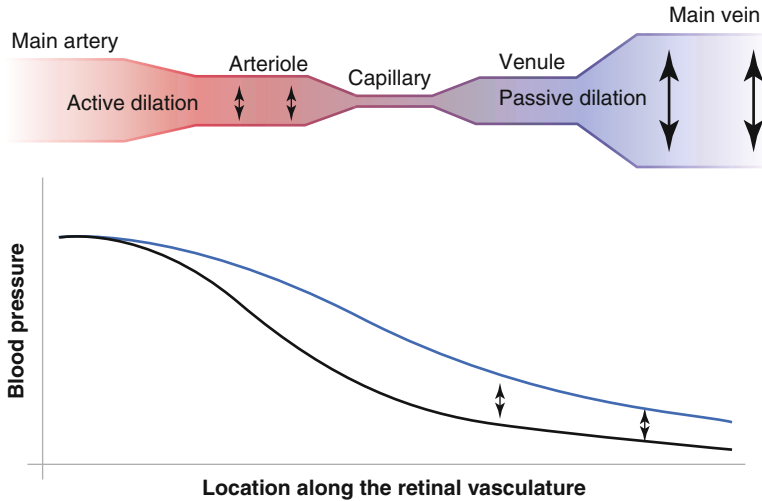


Fig. 2.6 Conceptual diagram of the decrease in the intravascular pressure as blood traverses the retinal vascular tree. The diagram illustrates heuristically, but not from actual experimental data, the effect of vessel length and radius as expressed in Poiseuille's law. That is, greater radius (dilation) is associated with a smaller pressure drop per unit length of vessel. The *black solid line* represents the normal drop in intravascular pressure. The *blue solid line* represents the autoregulatory response to hyperviscosity. The retinal arterioles dilate to keep blood flow con-

stant. As a result, the intravascular pressure experienced by the retinal capillaries and venules increases. By virtue of the increased transmural pressure, the retinal capillaries and venules passively dilate (Laplace's law). In retinal vein occlusion, when the transmural pressure rises enough, vascular wall integrity is lost and intraretinal hemorrhages appear. Before intraretinal hemorrhages appear, blood-retina-barrier breakdown is signaled by intraretinal edema (Redrawn from Menke⁴²)

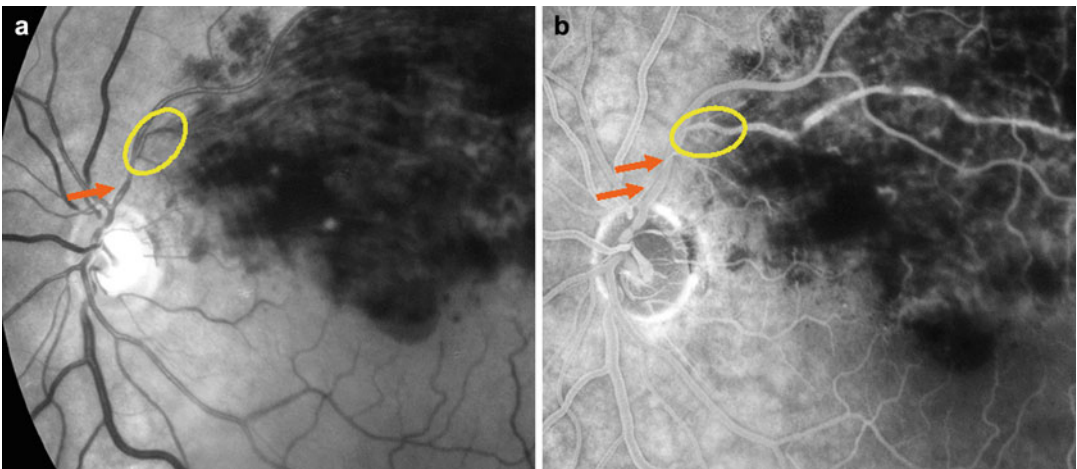


Fig. 2.7 Example of a patient with an acute branch retinal vein occlusion and its effects on venous caliber. **(a)** Monochromatic color fundus photograph showing the abrupt change in venous diameter at the occlusion. Distal to the occlusion, the vein is dilated (yellow oval). Proximal

to the occlusion, the venous diameter is threadlike and can barely be seen (orange arrow). **(b)** Frame from the late fluorescein angiogram showing the dilated vein upstream of the occlusion (yellow oval) and the thin venous segment downstream of the occlusion (orange arrow)

through autoregulation, retinal arterioles dilate. According to Poiseuille's law, the downstream retinal capillaries and venules experience a higher

intraluminal pressure because the pressure has dropped less over the arterial segment of the retinal vascular tree.

A Misapplication of Poiseuille's Law

Poiseuille's law has been misapplied, as well as properly applied, in the literature on RVO. For example, one finds the statement, "Poiseuille's formula would suggest that, in order to bring about a 50% reduction in pressure after emission from the lamina cribrosa, the diameter of the vein would have to be reduced by only some 16%."⁴⁴ Similar reasoning has been expressed elsewhere.⁴⁵ The problem with this statement and this line of reasoning is that Poiseuille's law applies to a segment of a cylindrical tube that has a constant diameter over its length, not a tube that has a changing diameter. Moreover, the pressure term referenced in the formula is the difference in pressure at the two ends of the segment, not the intravascular pressure at a given position within the tube. The more informative physiologic principle in this case (at least with respect to deductions concerning postlaminar CRV diameter) would be Bernoulli's principle (see Chap. 1).

In retinal vein occlusions of all types, the veins dilate upstream of the thrombus in concert with an increase in intraluminal pressure.⁴³ We are unable to observe what happens downstream to the thrombus in a CRVO, but in BRVO, the downstream intraluminal pressure falls, as indicated by reduction in the vessel radius (Fig. 2.7). In a total venous occlusion, the blood pressure throughout the retinal vascular tree proximal to the occlusion rises to the level of the central retinal artery pressure (or in the case of an eye with a cilioretinal artery, to the level of the posterior ciliary artery pressure).³⁷

2.2.1.3 Hemodynamics of Central Retinal Vein Occlusion

The intravascular pressure of the intraocular central retinal vein is higher than the intravascular pressure of the extraocular central retinal vein as long as the vein has not collapsed. The intravascular pressure of the intraocular central retinal vein approximately equals the IOP (Fig. 2.4b). There is no direct way to measure the intravascular pressure of the central retinal vein after it passes through the lamina cribrosa, but we can estimate it by virtue of the venous collapse phenomenon.⁴⁶ When the eye is compressed, either by an examiner's finger while performing funduscopy or by an ophthalmodynamometer, the intraocular pressure is raised, and at a certain point, the central retinal vein begins to pulsate. At this point, the intraocular pressure equals the intravascular pressure of the postlaminar central

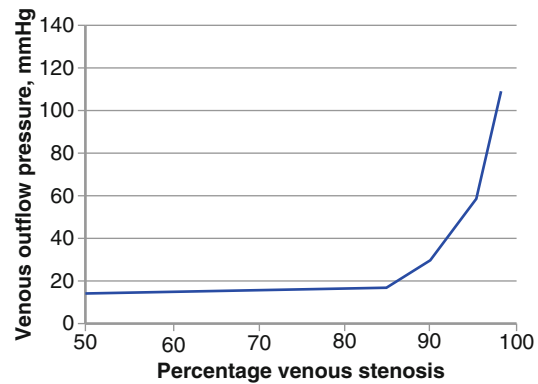
retinal vein at diastole. This is called the venous outflow pressure (VOP). If the pressure⁴⁷ is raised even further, the central retinal vein will collapse throughout the cardiac cycle. At this point, the intraocular pressure equals the intravascular pressure of the postlaminar central retinal vein at systole. The VOP in normal subjects is 11–22 mmHg but is elevated in patients with CRVO.⁴⁶ Because the intraneural central retinal vein is surrounded by subarachnoid space, it is exposed to the cerebrospinal fluid pressure of this space which is normally 4.4–7.3 mmHg. If the spinal fluid pressure increases to a level above the normal VOP of 22 mmHg, a state of relative retinal venous distention can be seen. Similarly, if the orbital tissue pressure rises, as, for example, in an orbital hematoma, the VOP can rise, and secondary retinal venous distention can be seen.

Ophthalmodynamometric measurement of the central vein collapse pressure is recorded in arbitrary units (AU). Mean central vein collapse pressures in more severe CRVOs, less severe CRVOs, BRVOs, and normal controls were 104 ± 25 AU, 58 ± 38 AU, 44 ± 26 AU, and 5 ± 8 AU, respectively, and each group was significantly different from the control group.⁴⁸ The data suggest that patients with BRVO have an abnormality not only at the involved arteriovenous crossing point but also at the lamina cribrosa. Otherwise, the central vein collapse pressure of the BRVO group should have been similar to that of the control group. In accord with this observation, many patients with BRVO in one eye develop CRVO in the same or fellow eye.^{48,49}

How Severe Must Central Venous Obstruction Be to Produce Symptoms?

There are no pathology specimens combined with clinical histories to provide a direct answer to this question. However, a physiologic model of ocular hemodynamics affords some insight. In this model, designed to resemble the retinal vascular circuit, pressures could be measured manometrically at key locations.⁴⁶ Using this model, the relationship of venous outflow pressure to percentage central venous stenosis was found to be exponential with no significant increase in VOP until stenosis reached 90% (Fig. 2.8).⁴⁶ We can infer that a thrombus must occlude 90% of the lumen of the central retinal vein before clinical signs such as venous distention will be observed.

Fig. 2.8 Diagram showing the relationship of venous outflow pressure and percentage of central retinal venous stenosis based on an experimental model. Milder (<85%) degrees of occlusion have no hemodynamic effects on retinal blood flow (Redrawn from Meyer-Schwickerath⁴⁶)



The Central Retinal Artery in Central Retinal Vein Occlusion

Although the central retinal vein (CRV) is the site of thrombosis in central retinal vein occlusion, the central retinal artery (CRA) is not normal. Color Doppler imaging has shown that the peak systolic blood flow velocity and vascular resistance (pulsatility index) are abnormal in the central retinal artery of patients with CRVO. The blood flow velocity is on average higher and the vascular resistance higher than in the unaffected fellow eyes or in healthy control eyes.⁵⁵ In 1965, the prevalent hypothesis explaining CRVO pathophysiology was that the central retinal vein and central retinal artery were occluded simultaneously.^{52,56,57} This hypothesis has subsequently been disproven based on several lines of evidence. In color Doppler imaging, the resistive index of the central retinal artery rises with an acute CRVO but falls back to normal by 3 months. This is a pattern to be expected if the decrease in central artery blood flow is a functional result of a primary blockage at the venous level, subsequently eased by widening of collateral veins or recanalization of the primarily thrombosed CRV.⁵⁰ The error in the hypothesis arose from extrapolating what was observed in young, healthy rhesus monkeys to the situation in elderly humans with vascular disease. In young monkeys, ligating the CRV produced no retinal hemorrhages, but ligating both CRV and CRA did. In elderly patients having comorbid arteriopathy, no such additional obstruction of the CRA is required to produce the clinical picture of CRVO. In that context, CRV occlusion alone is adequate to produce the clinical picture of CRVO. This historical vignette illustrates the hazards of extrapolating from animal models to human disease.⁵⁶

Thrombosis of the central retinal vein reduces blood flow velocity in the central retinal vein and artery of eyes with CRVO compared to fellow eyes and compared to normal control eyes.^{50,51} The velocity is reduced more in the CRV than the CRA and is lower in eyes with ischemic CRVO.⁵⁰ Central venous blood flow as assessed by color-flow mapping with spectral Doppler ultrasound remains decreased in untreated eyes for at least 1 year.⁵² Using Heidelberg retinal flowmetry, the retinal blood flow in the midperipheral retina, but not the macula, of patients with CRVO is lower compared to controls.⁵³ Collateral vessels allow the blood entering the retina to drain to the choroid. That is, the circulation from central retinal artery through central retinal vein is not a closed loop.⁵⁴

The prevailing hypothesis is that the more anterior the thrombus, the fewer the collateral vessels, the more sluggish the retinal perfusion, and the more ischemic the occlusion.⁵⁴ Over time, the carrying capacity of these collateral vessels increases, and retinal perfusion improves.⁵⁴

2.2.1.4 Hemodynamics of BRVO

In BRVO as in CRVO, blood flow is reduced to the involved region of the retina.^{11,51,58} In BRVO, scanning laser Doppler flowmetry shows decreases in microvascular blood volume, flow, and velocity compared to ipsilateral, nonoccluded areas of the retina; to symmetrical areas in normal fellow eyes; and to comparable areas in eyes of normal subjects.⁵⁹ As in CRVO, the development of retinal collaterals after BRVO presumably leads to improvement in retinal perfusion to the involved sector of retina, although there are no data to prove that deduction.

2.2.2 Oxygen Exchange in the Retina and Autoregulation

The retina exhibits the high rates of glycolysis necessary for the active transport of ions that generate gradients subserving neuronal action potentials.⁶⁰ The inner retina, defined as the zone from nerve fiber layer to inner nuclear layer, is supplied by vessels that derive from the central retinal

artery. This system is characterized by low flow, high vascular resistance, and high percentage oxygen extraction to support the retina's vigorous metabolism.^{31,61,62} Retinal blood flow is approximately 80 $\mu\text{l}/\text{min}$, and the retinal arteriovenous oxygen saturation difference is 30–40%.^{63,64}

By contrast, the outer retina, defined as the zone from the outer plexiform layer to the retinal pigment epithelium, derives its oxygen from the choroidal circulation, a high-flow system with low oxygen extraction.⁶⁵ Choroidal blood flow is approximately 800 $\mu\text{l}/\text{min}$, and the choroidal arteriovenous oxygen saturation difference is 3%.^{61,63} Mean oxygen saturation in normal human retinal arteries is $92.2 \pm 4.1\%$ compared to $57.9 \pm 9.9\%$ in retinal veins.⁶⁶

The normally high extraction of oxygen from the retinal blood supply has been studied in animal models. In cynomolgus monkeys breathing 21% oxygen, preretinal oxygen measurements with oxygen microelectrodes show a marked drop in oxygen tension as the distance from a retinal arteriole increases from <0.5 arteriolar diameter (termed juxta-arteriolar) to >5 arteriolar diameters away (termed intervascular). The juxta-arteriolar pO_2 was 44.4 ± 15.4 mmHg, whereas the intervascular pO_2 was 21.8 ± 0.6 mmHg.⁶⁷ This gradient decreased as distance from the retinal surface into the vitreous increased (Fig. 2.9).⁶⁰ There is also a steep gradient in oxygen tension across the thickness of the retina. The middle retina is significantly more hypoxic than the inner retina just as the perivenous retina is significantly more hypoxic than the juxta-arteriolar retina.⁶⁸ The oxygen tension within the retina is lowest in the outer plexiform layer, which represents the border zone between inner and outer retinas (Fig. 2.10). Therefore, the retina manifests three-dimensional oxygen concentration gradients under normal conditions.

The extraction of oxygen by the retina is affected by venous occlusion. For example, arteriolar oxygen saturation is the same in eyes with CRVO as in fellow eyes (mean saturation is 99% in both cases), but venous oxygen saturation is lower in eyes with CRVO ($49 \pm \text{SD}12\%$ vs. $65 \pm \text{SD}6\%$ in eyes with CRVO and controls, respectively).⁶⁷ With decreased retinal blood flow, the oxygen extraction from the blood by the retina

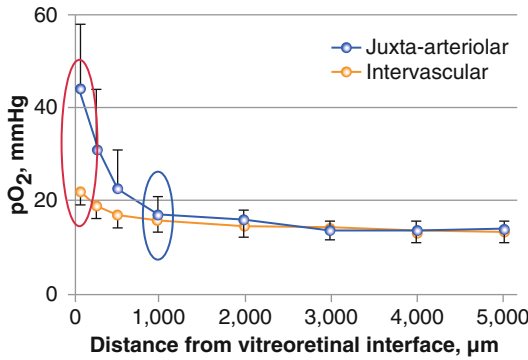


Fig. 2.9 Plot of preretinal oxygen tension in cynomolgus monkeys breathing 21% oxygen. Juxta-arteriolar is defined as a location of the oxygen microelectrode <0.5 major arteriolar diameter from a retinal artery. Intervascular is defined as >5 major arteriolar diameters from a retinal artery. Note the 22.6 mmHg gradient in oxygen tension from a juxta-arteriolar to an intervacular (more venous) location (red oval). This difference decreases rapidly with distance from the retinal surface. At a preretinal distance of 1 mm within the vitreous cavity, there is no difference (blue oval) (Redrawn from Pournaras et al.⁶⁸)

reduces the venous oxygen saturation more.⁶⁷ Accordingly, preretinal oxygen partial pressures are lower in experimental models of CRVO and BRVO, and there is lower tissue oxygen saturation in human CRVO and pig BRVO.^{47,60,64,69,70}

Autoregulation is the ability of the retinal vessels to maintain tissue perfusion despite variation in blood pressure. This characteristic of the retina is mediated by contractile mural wall pericytes and, possibly, endothelial cells.^{2,19,71} Retinal oxygen tension governs vascular autoregulation. A decrease in arterial pO_2 causes vasodilation of retinal arterioles.⁶⁰ The effects of systemic hypoxia on the pO_2 of the inner retina are buffered to a greater degree than in the avascular outer retina.⁶⁰ Besides pO_2 , autoregulatory roles are played by pCO_2 , pH, superoxide anions, endothelins, prostaglandins, adenosine, angiotensin, nitric oxide (NO), VEGF, and possibly other metabolic products.^{2,72-74} Retinal vessels have no sympathetic neural innervation, so vascular tone is controlled solely by autoregulation.

The most important autoregulatory mediator is nitric oxide, which causes retinal pericytes to relax. Increased vessel wall shear stress, increased blood flow, bradykinin, insulin-like growth factor 1,

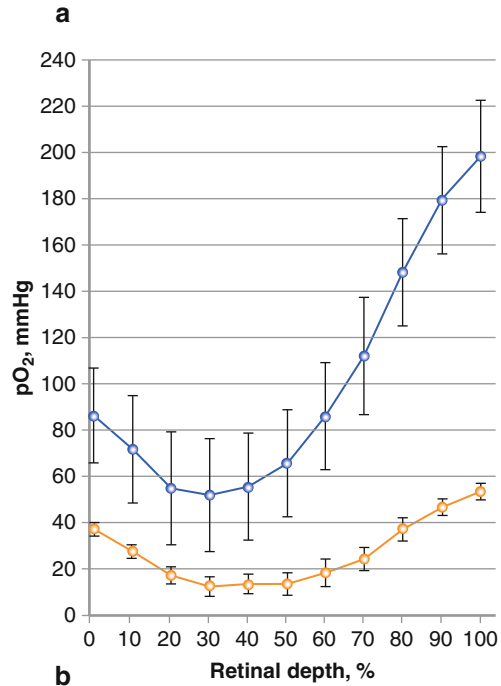
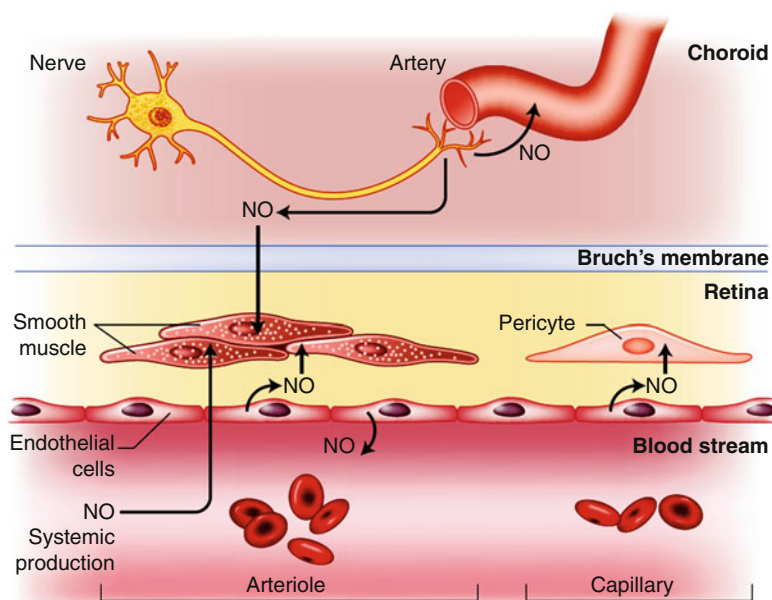


Fig. 2.10 (a) Transretinal oxygen partial pressure profile in a miniature pig. The yellow line represents measurement made with normoxia. The blue line represents measurements made with hyperoxia. The left side of the graph represents the vitread surface and the right side the choroidal interface. Under normoxia, the outer plexiform layer has the lowest partial pressure of oxygen at approximately 26% of the partial pressure of the retinal pigment epithelium and 38% of the partial pressure of the nerve fiber layer. Hyperoxia disproportionately increases the outer retinal oxygen partial pressure. (b) Diagram of the path of the oxygen microelectrode corresponding to the oxygen partial pressures shown in (a) (Redrawn from Pournaras⁶⁰)

acetylcholine, thrombin, and platelet products stimulate endothelial cells to release NO.^{72,74} Nitroergic neurons found in the choroid are an additional source of NO that may diffuse into the retina and stimulate vasodilation from the abluminal side of the vascular wall (Fig. 2.11).⁷²

Fig. 2.11 Hypothesized partial mechanism of autoregulation in retinal vessels mediated by nitrous oxide released from nitrergic neurons in the choroid and by nitrous oxide production in retinal vascular endothelium. In arterioles, the NO relaxes the mural smooth muscle fibers. In retinal capillaries, NO relaxes mural pericytes (Redrawn from Brown and Jampol⁷²)



Prostaglandins (PG) are a second class of autoregulatory mediators that can vasodilate (e.g., PGI_2) or vasoconstrict (e.g., $\text{PGF}_2\alpha$).⁷² Endothelin-1 is another mediator produced by retinal vascular endothelium and is the most potent vasoconstrictor known.⁷⁵ Endothelin-1 receptors are present on retinal pericytes, which contract upon endothelin exposure.⁷² The renin-angiotensin (RAS) system potentially interacts with vasoregulatory signaling in the retinal vascular endothelium. Angiotensin-converting enzyme (ACE) located in endothelial cells converts angiotensin I to angiotensin II. Angiotensin II degrades bradykinin, an activator of NO synthesis, and upregulates endothelin. ACE inhibitors increase bradykinin and reduce endothelin, both vasodilatory effects.⁷² The physiologic importance of the RAS system in human retinal vascular autoregulation has been suggested, but not demonstrated.⁷²

Coarse autoregulation occurs at the level of retinal arterioles, which constrict or relax to maintain the uniformity of segmental retinal blood flow. For example, in hyperviscosity syndromes, retinal venous blood flow velocity drops stimulating retinal arterioles to dilate and to maintain a constant blood flow (Fig. 2.6).⁴²

Pericytes then fine-tune retinal tissue perfusion at a microscopic level by changing capillary diameter.⁷⁶ At this level, increased extracellular oxygen tension mediates capillary constriction, whereas increased extracellular carbon dioxide, adenosine, and histamine constriction mediate dilation.⁷⁶ Pathways linking the state of cellular components of the blood to retinal vessel autoregulation have not been explained in detail. However, it has been observed that red blood cell count, hemoglobin level, hematocrit, and white blood cell count are correlated with central retinal venular equivalent and central retinal arteriolar equivalent (composite indices derived from vessel measurements made $\frac{1}{2}$ - to 1-disc diameter from the optic disc margin) and thus presumably also have a role to play in retinal vascular autoregulation.⁷⁷

In contrast to the retinal vasculature, the choroidal vasculature has neural innervation, but may also have supplementary autoregulatory potential (p. 8).⁷⁴ For example, exogenous heating causes an autoregulatory decrease in choroidal blood flow.⁷⁸

Therapies used in RVOs often take advantage of the autoregulatory system. For example, grid laser used in macular edema associated with

BRVO leads to an increase in inner retinal oxygen tension and autoregulatory vasoconstriction.⁴⁰ Concomitantly, the increase in retinal oxygen tension leads to a decrease in synthesis of VEGF. This causes the microvasculature to leak less because of reduced permeability and vasoconstriction.⁷⁹ Applying Starling's law, decreased capillary intravascular pressure from arteriolar vasoconstriction together with decreased capillary permeability implies decreased flow of water, ions, and macromolecules from the intravascular space into the extravascular space. Therapies such as intravitreal injection of microplasmin may also work through the mechanism of the oxygen pathway and autoregulation. Microplasmin induces a posterior vitreous detachment that is associated with an increase in vitreal oxygen concentration.⁸⁰

As covered in Chap. 1, the retinal vascular tree is fed by end arterioles, so the concept of a watershed zone is applicable.⁸¹ A watershed zone is a band of retina between the distribution of any two end arteries. Under conditions of normal blood supply, the existence of the watershed zones is not apparent. Normally in these zones, the blood is maximally deoxygenated but provides enough oxygen to the retina to maintain its transparency. However, during conditions of venous occlusion, the threshold for ischemia may be exceeded, causing loss of retinal transparency. The watershed zone becomes apparent as a band of whitening (Fig. 2.12). The whitened area of hypoxemic retina tends to occur temporally in the macula, which has a higher metabolic demand than the more peripheral retina. It occurs temporally because the vessel lengths are longer to this section of macula allowing greater oxygen extraction and enlargement of what has been termed the "anoxic corner" of the Krogh cylinder, the volume of cells that a length of capillary supplies with oxygen.⁸²

In addition to bands of ischemic retinal whitening at venous watershed zones, and far more common in RVO, cotton wool spots are a clinical sign of retinal ischemia. Cotton wool spots have been erroneously called focal infarcts, and some of them are, but most of them are not as elucidated by McLeod.⁸³ Most cotton wool spots are

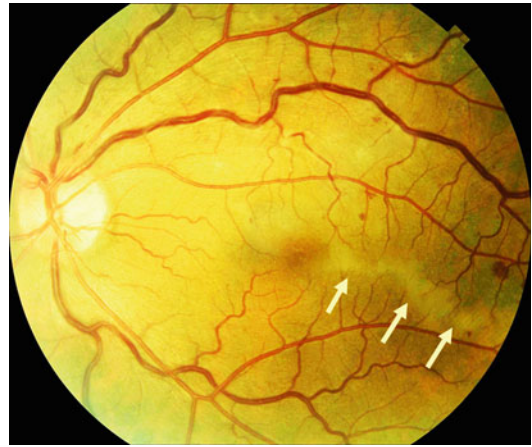


Fig. 2.12 Color fundus photograph of the left eye of a 45-year-old man with a nonischemic central retinal vein occlusion. The white band of ischemic retinal whitening occurs at a retinal watershed zone between the regions of the retina supplied by the superotemporal vascular arcade and the inferotemporal vascular arcade (yellow arrows)

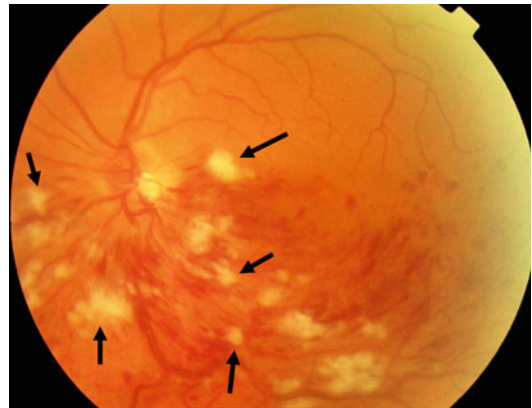


Fig. 2.13 Hemicentral retinal vein occlusion with a characteristic distribution of cotton wool spots (black arrows) that ring the optic disc along the distribution of the radial peripapillary capillaries. The annular band where these cotton wool spots cluster is termed the ischemic penumbra

sentinels of ischemia with focal axoplasmic flow stasis causing the white patches. Their characteristic distribution around the optic disc in RVO is explained by autoregulatory vasodilation immediately around the optic disc, shifting their site of occurrence more slightly peripherally to an ischemic penumbra (Fig. 2.13).⁸³

2.3 Macular Edema

From a public health perspective, macular edema is the most important clinical consequence of all forms of RVO. An understanding of the pathophysiology of macular edema is important for applying effective treatments and discovering new ones. The unique features of macular anatomy may have importance in development and resolution of macular edema in RVO. The formation and resolution of macular edema are both explained by Starling's law.

2.3.1 Macular Anatomy and Its Relationship to Macular Edema in Retinal Vein Occlusion

The capillaries in the macula are distributed in two strata within the inner retina with the exception of the single-level arrangement bordering the foveal avascular zone (see Chap. 1). This single level of capillaries is found within the ganglion cell layer.⁸⁴ Erythrocytes travel in the perifoveal capillaries in a pulsatile manner with speed in the range of 0.5–1.0 mm/s.⁸⁵ Farther from the fovea, the two levels of capillaries are found within the nerve fiber–ganglion cell layer and the inner nuclear cell layer. The more superficial capillary network is closer to the arteries, and the deeper network is closer to the venules. The outer retina throughout the macula is avascular and receives oxygenation by diffusion from the deeper choriocapillaris.⁶² The maximum distance between capillaries in the inner retina is approximately 65–100 μ , and the estimated maximal diffusion distance in the human macula consistent with normal function has been estimated to be approximately half this distance or approximately 45 μ .⁸⁴

Eighty percent of microaneurysms, which seem to be a microvascular response to vascular endothelial growth factor (VEGF) generated from hypoxic retinal tissue, originate in the inner nuclear layer and its border zones.⁸⁶ The larger microaneurysms tend to occur in this zone, and

smaller ones in the nerve fiber–ganglion cell layers. Microaneurysms range in size from 13 to 136 μ .⁸⁶ Microaneurysms are particularly frequent on the edges of nonperfused retina in RVO, consistent with the hypothesis that they are a secondary reaction to hypoxia and increased local vascular endothelial growth factor concentration.

In macular edema associated with RVO, it is common for the central macula, including the foveal vascular zone, to be thickest, an inversion of the normal relationship. Although the underlying reason has not been established, one hypothesis is based on the avascularity at the center of the macula. In other regions of the macula, edema fluid can escape the extracellular space in two ways – outward to the choroid via the pumping mechanism of the retinal pigment epithelium and back into the intravascular space through the walls of capillaries, the direction reverse to salt and water egress from intra- to extravascular space in the more proximal microvasculature (Fig. 2.14). At the center of the macula, the only mechanism for egress of extravascular fluid is

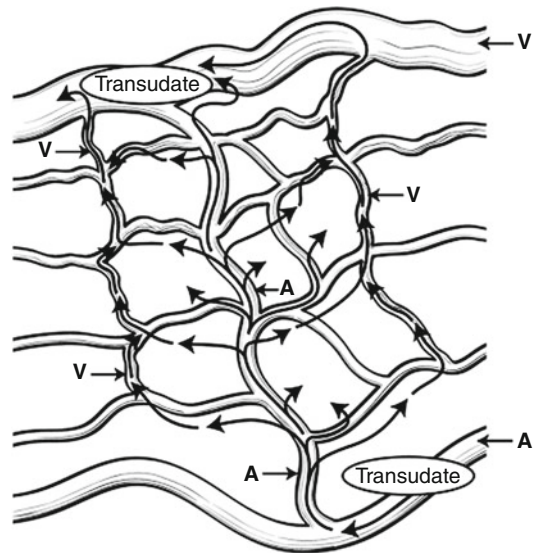


Fig. 2.14 Diagram indicating one pathway for salt and water within the retina. Under the influence of higher intravascular pressure in the arterioles (A), salt and water pass out of the vessels (transudate) and into the extracellular space of the retina, then returning to the intravascular space in part by entering the venular side of the circulation (V) which has a lower intravascular pressure

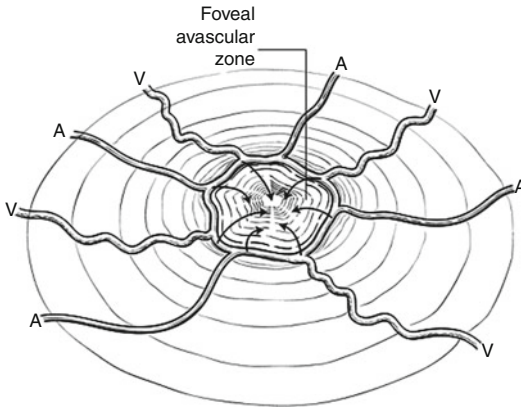


Fig. 2.15 Diagram indicating the different situation of the center of the macula. There is no venous side of the vasculature in this one location in the retina, thus salt and water can exit the vascular space from the capillaries, but can only leave the extracellular space via the action of the retinal pigment epithelial pump and not via reentry into the venules which are missing in this location

that of the retinal pigment epithelial (RPE) pump, which may explain the greater accumulation of edema fluid and increased retinal thickness at this location (Fig. 2.15). A fundus sign of the preferential accumulation of edema fluid in the center of the macula is the appearance of the macular lipid star (Fig. 2.16). As the RPE pumps salt and water from the retinal extracellular space to the choroid, lipoproteins contained in the extracellular fluid are left behind as yellow exudates that must be cleared much more slowly by macrophages. In many cases of RVO, a serous retinal detachment is present which is usually localized under the fovea. Although the explanation for the subfoveal location of fluid is conjectural, one possibility is the absence of the normal return pathway for extracellular fluid via the intraretinal venules in this one location of the retina.

Muller cells are important in transporting water from the extracellular space into the retinal capillaries of the inner retina.⁸⁷ Their density in the macaque monkey is five times greater in the parafovea than the retinal periphery.⁸⁸ The colocalization of Muller cells with the retinal regions most affected by edema suggests that Muller cell dysfunction contributes to macular edema associated with RVO. Moreover, Muller cells proliferate in epiretinal membranes, which



Fig. 2.16 A macular lipid star is a fundus sign in macular edema and indicates that the center of the macula is a preferential site for accumulation of extracellular fluid

can exert traction on microvessels and possibly increase their permeability, exacerbating macular edema.

Within the retina, the synaptic portion of the outer plexiform layer and the entire inner plexiform layer comprise the two highest resistance barriers to the diffusion of interstitial fluid from the inner retina outward toward the choroid.⁸⁹ At these layers, the density of junctional complexes between cells and the tortuousness of cellular processes combine to impede most stringently the extracellular flow of water and solutes.⁹⁰

2.3.2 Starling's Law

Starling's law states that the equilibrium state of fluid transfer between the intravascular and extravascular spaces is characterized by the equation

$$\Delta P - \Delta Q = 0,$$

where

ΔP = intravascular pressure within microvessels of retina minus the extravascular tissue pressure
 ΔQ = intravascular oncotic pressure minus the intraocular pressure

Hypothetical intravascular pressures in nonischemic CRVO with macular edema

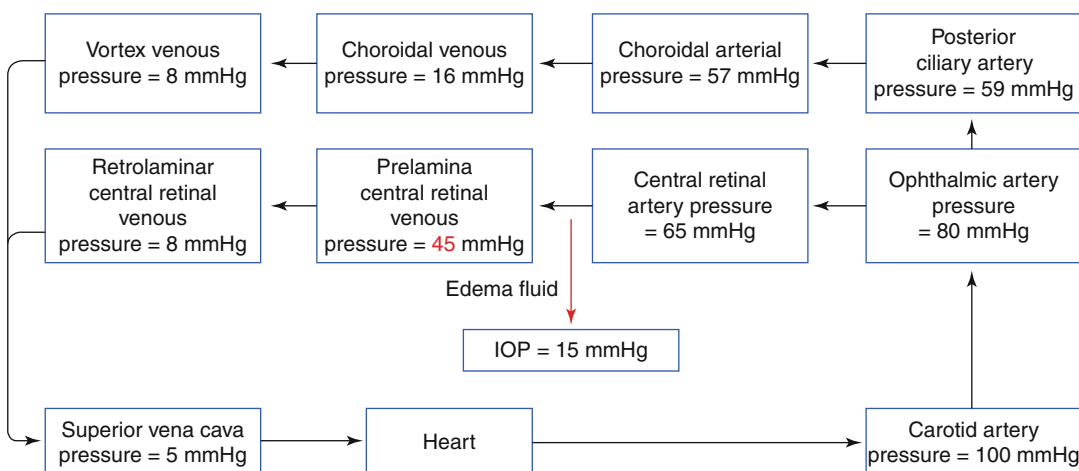


Fig. 2.17 Hypothetical intravascular pressures in nonischemic CRVO with macular edema. Diagram of hypothetical intravascular pressures found in a case of nonischemic CRVO with macular edema. Refer to Fig. 2.4b as the normal baseline in interpreting this diagram. The change is the elevation of the prelaminar cen-

tral retinal venous pressure from 15 to 45 mmHg. This acute change, also experienced by the retinal capillaries upstream of the thrombus, disrupts the previous Starling's equilibrium and leads to transudation of salt and water into the extracellular space working against a pressure of 15 mmHg (red arrow)

Starling's law accounts for many common clinical observations (Fig. 2.17). For example, in a nonischemic CRVO, the prelaminar central venous pressure is acutely elevated. In the hypothetical case illustrated in Fig. 2.17, the venous pressure has suddenly increased from 15 (Fig. 2.4b) to 45 mmHg. Before the CRVO, $\Delta P_{\text{preCRVO}} = \Delta Q_{\text{preCRVO}}$, and after the CRVO, $\Delta P_{\text{postCRVO}} > \Delta Q_{\text{postCRVO}}$ because ΔP has increased. This change disrupts the previous equilibrium and leads to transudation of salt and water out of the vascular space and into the extracellular space. Arteriolar constriction from any cause (e.g., after breathing 100% oxygen or injecting bevacizumab) causes ΔP to decrease relative to its previous state of equilibrium, and thus, fluid moving from the vascular compartment toward the extravascular compartment diminishes.

Macular edema in RVO often shows diurnal variation with edema worse in the morning and improving late in the day. In one study, median macular thickening in CRVO decreased by 96 μ during waking hours.⁹¹ Starling's law explains the clinical phenomenon. When a patient with a RVO is recumbent, the intravascular pressure in

the retinal capillaries increases compared to when the patient is erect, especially if retinal autoregulation is dysfunctional as it is in patients with diabetes.⁸⁹ The increased pressure will tend to drive more fluid from the vascular to the extravascular space.⁹¹ Other physiologic mechanisms may augment the effects of Starling's law. The oxygen consumption of the retina is higher in the dark-adapted state, which could increase relative retinal hypoxia during sleep.⁹¹ Nocturnal hypotension may also reduce blood flow to the retina even more and worsen hypoxia.⁹¹

2.3.3 The Retinal Pigment Epithelial Pump

In most discussions of macular edema associated with RVO, the role of the retinal pigment epithelial (RPE) pump is comparatively neglected because it is difficult to study. Extracellular fluid travels from the retina outward toward the choroid primarily under the influence of the RPE pump action.⁹² Figure 2.18 illustrates the current

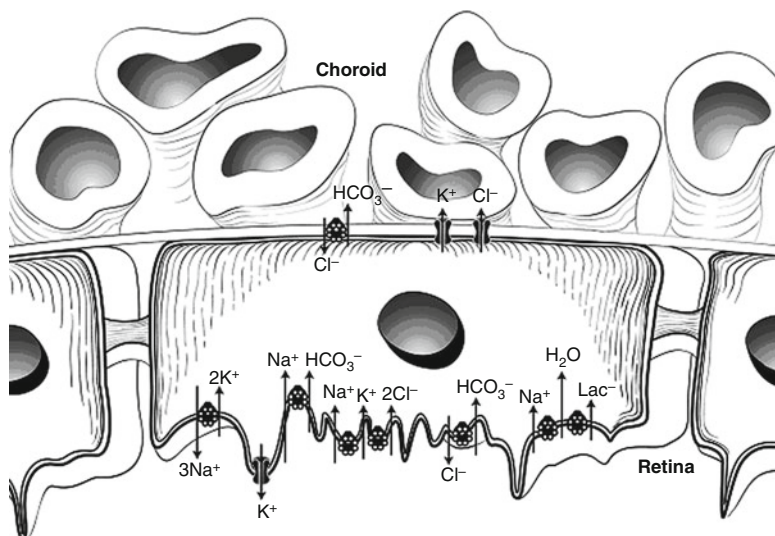


Fig. 2.18 Model of the retinal pigment epithelial pumping mechanism. The RPE cells are connected by zonula occludens which restrict the extracellular flow of ions and water back from the choroid toward the retina via the intercellular space between RPE cells. The primary energy-dependent pump is the apical (retina side) sodium-potassium, electrogenic pump (*left side of the cell*). Other active transport systems derive the energy they require to

run from the electrochemical gradients built up by this primary pump. In the apical membrane, independent sodium-bicarbonate, sodium-potassium-chloride, chloride-bicarbonate, and sodium-lactate-water transport sites have been described. In the basal membrane, a chloride-bicarbonate cotransporter exists. Passive conductance channels for potassium and chloride also exist as shown (Redrawn from La Cour⁹³ and Quintyn⁹²)

conception of ionic and fluid transport across the RPE into the choroid. An active sodium-potassium pump is present on the apical membrane of the RPE that exchanges three sodium ions toward the extracellular space for two potassium ions toward the RPE cytoplasm. An electrochemical gradient is generated by the asymmetry in the ionic exchange ratio, and this gradient powers other active transport mechanisms of which several have been described. Independent sodium-potassium-chloride and sodium-bicarbonate cotransport sites exist on the apical RPE membrane. An apical sodium-proton exchanger exists. These actively concentrate chloride and bicarbonate intracellularly. On the basal RPE membrane, separate sites exist for chloride and potassium ion egress as well as a chloride-bicarbonate cotransporter.^{92,93} Physiologic and pharmacologic modulation of fluid transport across the RPE is possible. Hypoxia decreases active transport across the RPE. Epinephrine applied to the apical RPE surface increases RPE

transport. Acetazolamide increases transport, whereas furosemide decreases it. In extremely high concentrations not achieved clinically, digoxin reduces RPE transport. The possible influence of drugs commonly taken by patients with RVO in altering the response to therapy for macular edema associated with RVO has been unexplored to date.

In RVO with macular edema, the RPE pump is overwhelmed by the exudation of serum, and macular swelling results.⁹⁴ Because salt and water are pumped from the retinal compartment out toward the choroid, but associated serum lipoproteins are not, hard exudates derived from the lipoproteins accumulate in the retina. They often appear in rings centered on leaking clusters of microaneurysms and dilated capillaries. In diabetic macular edema, the permeability of the retinal capillaries increases approximately 12-fold, but the activity of the pigment epithelial pump increases only twofold, a mismatch resulting in extracellular fluid accumulation.^{40,94} Although

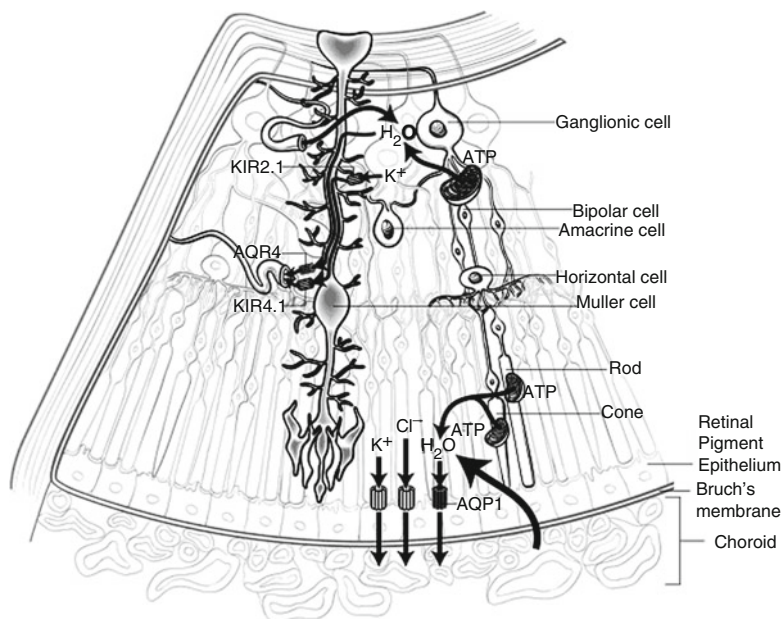


Fig. 2.19 Schematic depicting pathways for water transport in the retina. Water is generated in the retina by oxidative synthesis of adenosine 5'-triphosphate (ATP) that generates carbon dioxide and water (H_2O). The Muller cell has processes that wrap around retinal microvessels. Bidirectional potassium channels called Kir4.1 are present in the Muller cell membranes abutting these microvessels. Muller cells also possess unidirectional potassium channels called Kir2.1 abutting the extracellular space that allow passage of potassium from the neuroretinal cells into the Muller cell. Aquaporin 4 (AQP4) water channels

allow the osmotic cotransport of water to follow potassium movement. The retinal pigment epithelium also actively transports potassium and chloride from the retina to the choroid with water cotransport occurring via aquaporin1 (AQP1) channels. If the Kir4.1 channels are decreased in RVO (as in diabetic macular edema), but not the Kir2.1 unidirectional potassium channels or the RPE potassium transport channels, the net effect could be Muller cell swelling – intracellular edema (Redrawn from Reichenbach and colleagues⁹⁵)

not examined in RVO, it is plausible that a similar asymmetry in vascular hyperpermeability versus RPE pumping is operative.

Our discussion of macular edema associated with RVO to this point has concerned extracellular edema, also called vasogenic edema. In addition to extracellular edema, a concept of intracellular edema exists which may be relevant, although it has been less studied.^{87,95} Water transport out of the retina occurs via retinal pigment epithelial active transport of potassium and chloride and passive cotransport of water across aquaporin1 channels. Less recognized, however, is transport of water into retinal microvessels via Muller cells. Muller cells possess a unidirectional potassium channel called Kir2.1 that allows extracellular potassium derived from

neuronal firing to pass into the Muller cell, but not out of it. In addition, Muller cells have a bidirectional potassium channel called Kir4.1 that allows Muller cell intracellular potassium to flow into vessels around which Muller cell processes are wrapped (Fig. 2.19). It is possible that in RVO, as in diabetic macular edema, Muller cells may take up potassium from the extracellular space but have diminished ability to discharge the potassium into the retinal microvessels. Because water osmotically follows solute, the Muller cells can swell, a situation termed intracellular edema. Whereas the evidence for intracellular edema appears to be substantial in diseases of the brain, models for intracellular edema in the retina have been less well investigated.^{95,96}

2.3.4 Molecular Signaling in Macular Edema

The list of molecules known to regulate vascular permeability, angiogenesis, and angioinhibition continues to grow, as does the complexity of their interactions (Table 2.3). The particular effects of a molecule depend on the context. For example,

transforming growth factor (TGF) β can be an angioinhibitor, a promoter of angiogenesis, or a chemoattractant depending on what other molecules are present. Pigment epithelial derived growth factor (PEGF) can be a pro- or antiangiogenic factor depending on the molecular environment.^{97,98} The interaction of the components in the cytokine network is just beginning to be unraveled.

Relevant Molecular Biologic Terminology

The terms cytokines, chemokines, cell signaling, upregulation, and downregulation are frequently used in discussions of ocular physiology. Because the terms are ubiquitous and nuances of meaning possibly unclear, it may help to define them here.

Cytokine – a small protein or peptide that is involved in intercellular communication; in the context of ocular physiology, cytokines are secreted by cells of the retina and by immune cells.¹⁰⁰

Chemokine – a cytokine that induces directed chemotaxis, recruits leukocytes to sites of inflammation, promotes inflammation, and promotes stem-cell survival, development, and homeostasis.¹⁰¹

Cell Signaling – a complex system of communication between cells that involves secretion of small molecules and response to them within the microenvironment of a tissue. Cell signaling is involved in tissue development, response to injury, repair, and maintenance of homeostasis.

Upregulation and Downregulation – processes for changing the quantity of a molecule in response to a change in an external variable, for example, a change in the rate of transcription of part of the genome. Another example would be increasing (upregulation) the number of platelet receptors for collagen in response to smoking.

The retina has vascular and avascular tissues in apposition implying close regulation of angiogenesis and angiomaintenance.⁹⁹ In the normal mature retina, retinal capillary endothelial cells are quiescent, and levels of VEGF are absent or vanishingly low.¹⁰⁰ The absence of all vessels in certain zones of the retina, such as adjacent to retinal arterioles, is presumably governed by potent, but poorly understood, processes of angioinhibition.²

2.3.4.1 Vascular Endothelial Growth Factor

The most important and studied cytokine in retinal physiology is VEGF. VEGF is

multifunctional; its actions depend on the cellular context and microenvironment. VEGF is secreted in four homodimeric forms resulting from alternative ribonucleic acid (RNA) splicing.¹⁰¹ Two forms – VEGF 121 and VEGF 165 – are freely diffusible within the vitreous cavity.¹⁰² VEGF 121 is a secreted, diffusible protein that is essential for normal retinal function, acting as a survival factor for retinal neurons.⁹⁷ In rats, chronic paninhibition of VEGF with anti-VEGF antibodies led to a loss of retinal ganglion cells.¹⁰³ Selective blockade of the VEGF 164 isoform (the rat homologue of human VEGF 165), but not the VEGF 120 isoform (the rat homologue to human VEGF 121), did not lead to

Table 2.3 Proangiogenic and antiangiogenic factors

Proangiogenic factors	Antiangiogenic factors
Angiogenin	Angiostatin (plasminogen fragment)
Angiopoietin	Antiangiogenic antithrombin III
Developmentally regulated endothelial locus-1 (Del-1)	Cartilage derived inhibitor (CDI)
Acidic fibroblast growth factor (aFGF)	CD59 complement fragment
Basic fibroblast growth factor (bFGF)	Endostatin (collagen XVIII fragment)
Follistatin	Fibronectin fragment
Granulocyte colony stimulating factor (G-CSF)	Growth-regulated oncogene (Gro-β)
Hepatocyte growth factor (HGF)/scatter factor (SF)	Heparin hexasaccharide fragment
Interleukin-8 (IL-8)	Heparinases
Leptin	Human chorionic gonadotropin (hCG)
Midkine	Interferon α/β/γ
Pigment epithelium derived growth factor (PEDF)	Interferon inducible protein (IP-10)
Placental growth factor	Interleukin 12
Platelet-derived endothelial cell growth factor (PDEC GF)	Kringle 5
Pleiotropin (PTN)	2-Methoxyestradiol
Proliferin	Pigment epithelium derived growth factor
Transforming growth factor α (TGF-α)	Placental ribonuclease inhibitor
Transforming growth factor β (TGF-β)	Plasminogen activator inhibitor
Tumor necrosis factor α (TNF-α)	Platelet factor 4 (PF4)
Vascular endothelial growth factor (VEGF)	Prolactin 16-kDa fragment
	Proliferin-related protein (PRP)
	Retinoids
	Tetrahydrocortisol-S
	Thrombospondin-1 (TSP-1)
	Tissue inhibitors of metalloproteinases (TIMPs)
	Transforming growth factor β (TGF-β)
	Vasculostatin
	Vasostatin (calreticulin fragment)

Adapted from Ng and Adamis⁹⁷

Proangiogenic and antiangiogenic factors

retina ganglion cell loss.¹⁰³ VEGF 165 is the isoform most closely associated with pathological neovascularization.⁹⁷ VEGF 165 has moderate heparin affinity and is detected on cell surfaces and in the extracellular matrix. A splice variant of VEGF 165, termed VEGF 165b, has an anti-angiogenic rather than pro-angiogenic effect.¹⁰⁴ The relative ratios of VEGF 165 and VEGF 165b are partially regulated by the oxygen concentration.¹⁰⁴ VEGF 189 contains an additional heparin-binding domain that binds to the protein heparin sulfate on the cell surface and basement membrane.¹⁰⁵ VEGF 208 also binds to cell surface receptors or basement membrane proteoglycans containing heparin.¹⁰⁶ VEGF 189 and VEGF 208 can be cleaved by plasmin, thereby releasing active diffusible VEGF.⁹⁹

VEGF is undetectable in the aqueous of the normal eye, but decreased retinal blood flow and tissue hypoxia in RVO lead to increased VEGF production by retinal pigment epithelial cells, capillary endothelial cells, pericytes, Muller cells, astrocytes, ganglion cells, and other cells of the inner nuclear layer.¹⁰⁷⁻¹⁰⁹ In a primate model of RVO, the highest levels of VEGF expression were in the inner retinal layers (ganglion cell and inner nuclear layer).^{105,110,111} In pathological specimens of eyes with CRVO and neovascular glaucoma, VEGF mRNA is found in the inner nuclear layer and in some cases in the ganglion cell layer and outer nuclear layer.¹¹² VEGF is not found in photoreceptors from retinas exposed to hypoxia.¹¹³ The source of VEGF is within the eye, since aqueous concentrations of VEGF after RVO show

no correlation with serum VEGF concentrations.¹¹⁴ VEGF concentration rises in vitreous fluid in ischemic RVO and is approximately 60% higher there than in the aqueous.¹¹⁰

VEGF is the major vasopermeability factor that disrupts the blood–retina barrier in RVO by inducing fenestrations in capillaries and venules.^{99,115} VEGF effects begin with binding to two receptors, VEGFR-1 and VEGFR-2. The two receptors mediate different effects. VEGFR-2 is thought to be the principal receptor involved in angiogenesis and vasopermeability signaling pathways.⁹⁷ In cultured vascular endothelium, hypoxia induces VEGFR-2 expression, but TGF- β decreases expression.⁹⁹ VEGF activates VEGFR-2, causing phosphorylation of occludin and tight junction protein (ZO-1) and changes in the protein content of tight junctions of retinal vascular endothelial cells.¹¹⁶ The blood–retina and blood–aqueous barriers are disrupted in BRVO, and more so in CRVO, as demonstrated by vitreous fluorophotometry and aqueous flare measured by photometry.¹¹⁷ Average vitreal concentration of VEGF in CRVO is 8.6 ng/ml in CRVO, compared to 2.0 ng/ml in BRVO and 0.26 ng/ml in eyes without RVO.¹⁰⁴ A lower concentration of intraocular VEGF is required to increase vascular permeability than that required to induce neovascularization. Aqueous concentrations of VEGF of 0.3 ng/ml produce a breakdown of the blood–ocular barrier and increase aqueous serum albumin concentration, but are not sufficient to induce retinal or iris neovascularization.¹¹⁷ An average VEGF concentration of 5 ng/ml is found in the vitreous of human eyes with active neovascularization.¹¹⁰

VEGF is also the most important cytokine mediating intraocular neovascularization after RVO. In a primate model of intraocular neovascularization after laser-induced retinal ischemia, VEGF mRNA levels increased in the ischemic retina, intraocular VEGF protein levels were temporally and spatially correlated with neovascularization, and neovascularization could be blocked with injection of anti-VEGF antibodies.^{111,118} The angiogenic effects of VEGF depend on the presence of other modulating cytokines. Thus, the presence of TNF- α in the environment is necessary for human microvascular endothelium to grow tubular capillary structures.⁹⁹

VEGF is a proinflammatory cytokine and a chemoattractant for endothelial cell precursors.⁹⁷ VEGF increases vascular endothelial intercellular adhesion molecule-1 (ICAM-1) expression, which in turn increases the adhesion of neutrophils and monocytes to the vascular endothelium. This pathway, together with VEGF-induced retinal endothelial swelling, is known to be associated with decreased macular capillary blood flow velocity and might exacerbate capillary nonperfusion.^{41,101,119–122} VEGF induces expression of thromboplastin, a procoagulant molecule that might also aggravate capillary nonperfusion.¹²³

Many cytokines upregulate VEGF, including transforming growth factors (TGFs) α and β , basic fibroblast growth factor (bFGF), epidermal growth factor (EGF), keratinocyte growth factor, platelet derived growth factor (PDGF), insulin-like growth factor (IGF)-1, PGE2, TNF- α , angiotensin II, and many others.^{97,99} Hypoxia increases transcription of the VEGF gene and stabilizes VEGF mRNA.¹²⁴ Hypoxia-inducible factor (HIF)-1 α is the crucial mediator in this process. In the presence of oxygen, HIF-1 α is degraded. However, in hypoxia, HIF-1 α is stabilized, which stimulates VEGF gene transcription.¹²⁵ VEGF gene expression is increased in ischemic inner retina in animal models of RVO.¹¹¹ The critical pO₂ below which VEGF production is upregulated is not known.⁶⁰ Systemic hyperoxia lowers retinal VEGF gene expression that has been upregulated by BRVO.⁶⁸

Manipulation of intraocular VEGF activity has worried some because of evidence that VEGF 121 is a survival factor and required for the maintenance of normal blood vessels, at least during development.¹²⁶ To date, no evidence suggests that in adults with RVO, blockage of intraocular VEGF activity harms the retina.¹²⁷

2.3.4.2 Other Retinal Cytokines with Lesser Roles

Aside from VEGF, vasopermeability factors include interleukin (IL)-6, IL-8, TNF- α , intercellular adhesion molecule-1 (ICAM-1), and monocyte chemotactic protein (MCP)-1.^{128,129} IL-6 directly increases capillary permeability by

rearranging actin filaments in gap junctions between adjacent cells and indirectly by increasing the expression of VEGF.^{108,130,131} IL-8 is a chemokine that attracts and activates neutrophils and T lymphocytes, but not monocytes. It has both angiogenic and vasopermeability effects. IL-8 is produced by endothelial cells and glial cells in retinas with ischemic angiogenesis and is secreted by RPE cells in response to proinflammatory factors such as TNF- α , IL-1 β , IL-7, and Toll-like receptors.¹³² VEGF induces endothelial cell production of IL-6 and IL-8.¹³³ ICAM-1 mediates interactions of leukocytes and vascular endothelium and may be responsible for the leukocyte trapping and release of cytokines by leukocytes that increase vascular permeability.¹²⁹ ICAM-1 may also have a role in progressive ischemia that develops in some RVOs.¹²² MCP-1 is a chemokine that attracts and activates monocytes, memory T cells, dendritic cells, and lymphocytes, but not neutrophils, to sites of tissue injury.^{134,135} IL-8 and MCP-1 are both regulated by nuclear factor-kappa β (NF-KB), a cytokine involved in response to stress, free radicals, ultraviolet radiation, and bacterial and viral antigens.¹³⁶

Erythropoietin (EPO) is a glycoprotein that has erythropoietic as well as angiogenic functions. It seems to have a neuroprotective function in the retina and may mitigate macular edema, but may also exacerbate angiogenesis.^{137,138} It is made in the inner retina and in the retinal pigment epithelium.¹³⁷ As with VEGF, production of EPO is regulated by HIF-1 α . Inconsistent information has been published on vitreous concentrations of EPO in RVO. Vitreous EPO was elevated in both CRVO and BRVO compared to vitreous levels found in eyes undergoing surgery for macular pucker and macular hole in two studies, but no differences were found in a third study.¹³⁷⁻¹³⁹ Vitreous erythropoietin and VEGF concentrations are correlated in CRVO and BRVO.^{137,138} In a mouse model, exposure to EPO had a biphasic effect, protecting against retinal neovascularization during hypoxia before neovascularization developed, but exacerbating neovascularization when exposure occurred after the neovascularization had begun.¹⁴⁰

Aqueous placental growth factor (PGF) concentrations are elevated in eyes with ischemic

CRVO that develop NVI. Placental growth factor may facilitate the effects of VEGF to induce or perpetuate intraocular neovascularization in CRVO.¹¹⁶

Basic fibroblast growth factor (bFGF) is another locally produced cytokine involved in angiogenesis. It is a 146-amino-acid polypeptide that is angiogenic at 1–10 ng/ml concentrations and is produced by vascular endothelial and retinal pigment epithelial cells.^{141,142} Unlike VEGF, bFGF is not upregulated by hypoxia, and it seems to have complex interactions with extracellular matrix.¹⁴³⁻¹⁴⁵

Angiostatic factors include angiostatin, TGF- β , corticosteroids, monokine induced by interferon gamma (MIG), some interleukins, and interferon-gamma-inducible 10 kD protein (IP-10).^{2,146} MIG levels are high in patients with BRVO with macular edema. It has been suggested that it has a role in protecting the blood–retina barrier. Unlike VEGF and IL-8, its preoperative level is not correlated with the amount of decrease of edema after vitrectomy with internal limiting membrane peeling.¹⁴⁶ Pigment epithelial derived growth factor (PEDF) counterbalances the effects of VEGF on angiogenesis, but it is less clear if it does so with respect to vasopermeability.^{143,147} VEGF may upregulate PEDF expression as a feedback control mechanism.¹⁴⁷

Some cytokines may be markers for underlying systemic atherosclerosis. For example, mean serum leptin levels are higher in patients with BRVO than control patients.¹⁴⁴ Evidence of intraocular production of leptin in CRVO with neovascularization also exists, but details regarding its role are uncertain.¹⁴⁵

2.3.4.3 Molecular Signaling in BRVO

In BRVO, these factors have been found to be elevated in the vitreous, aqueous, or both compared to control patients without BRVO: VEGF, IL-6, IL-8, MIG, MCP-1, EPO, macrophage-inhibitory protein (MIP)-1 β , ICAM-1, and IP-10.^{117,129,133,136,137,146,148-161} Aqueous levels of VEGF have been found to correlate with vitreous levels of VEGF. Aqueous and vitreous levels of

VEGF and ICAM-1 and vitreous levels of EPO and IL-6 have been found to correlate with degree of retinal nonperfusion and severity of macular edema.^{129,137,148,149,151,155} Vitreous levels of IL-8 and MCP-1 are correlated in BRVO.¹³³ Vitreous levels of IL-6 have been found to correlate with the area of retinal nonperfusion.¹⁴⁹ Preoperative levels of VEGF and IL-8 have been found to correlate with the magnitude of reduction in macular thickness after vitrectomy for BRVO with macular edema.¹⁴⁶ VEGF levels are higher in eyes with BRVO that develop subretinal fluid than in eyes that develop cystoid macular edema without subretinal fluid.¹⁵⁰ Vitreous levels of soluble ICAM-1 have been found to correlate with perifoveal capillary blood flow velocity in a study of patients with pooled RVO, mostly BRVO. Vitreous VEGF concentration was not correlated with perifoveal capillary blood flow velocity.¹⁴³ The increased concentrations of the inflammatory mediators IL-6, IL-8, and MCP-1 suggest a common pathway involving inflammation in BRVO.¹³⁶

Reports of vitreous PEDF levels have been inconsistent in BRVO: both elevated and decreased levels have been reported.¹²² PEDF levels have been reported to correlate negatively with vitreous VEGF levels and severity of macular edema in BRVO.¹²²

The following molecules are not elevated in BRVO:

- (Growth factors) EGF, bFGF, G-CSF, and GM-CSF
- (Chemokines) eotaxin, MIP-1 α , MIP-1 β , RANTES
- (Cytokines) IL-1 β , IL-2, IL-4, IL-10, IL-17, IFN- γ , and TNF- α ¹⁰⁰

In BRVO, upregulation of VEGF continues for at least 2 years whether collateral vessels develop or not. The evidence for this is based on the need to block VEGF by monthly injections of ranibizumab.¹⁵⁴

Nonhuman primate models in which intravitreal VEGF levels increase after branch venous occlusions do not show preretinal neovascularization, suggesting that cytokines other than VEGF are required for the clinical finding of posterior segment neovascularization in humans after BRVO.⁹⁹

2.3.4.4 Molecular Signaling in CRVO

The situation regarding molecular signaling in CRVO resembles that in BRVO. Differences between the two conditions relate to the fact that fewer factors have been investigated in CRVO. In CRVO, elevated levels of these cytokines have been found: VEGF, soluble vascular endothelial growth factor receptor-2, IL-8, IL-6, erythropoietin, and MCP-1.^{130,137,155,156} Vitreous VEGF levels correlate with severity of macular edema and ischemia in CRVO.^{130,136,137,157} The vitreous levels of IL-6 and VEGF are elevated in CRVO compared to controls, but the serum levels are not, implying intraocular production of these factors.¹³⁶ The vitreous levels of IL-6 are correlated with the severity of macular edema of CRVO.¹³⁰ Elevated levels of IL-6, IL-8, and MCP-1 were highly correlated in one study, suggesting a common pathway involved in their common upregulation.¹³⁶ These molecules are not elevated in CRVO:

- (Cytokines) IL-1 β , IL-2, IL-4, IL-5, IL-10, IL-17, IFN- γ , and TNF- α
- (Chemokines) eotaxin, MIP-1 α , MIP-1 β , and RANTES
- (Growth factors) EGF, bFGF, G-CSF, and GM-CSF¹³⁶

In human CRVO, a correlation exists between aqueous VEGF concentration and the onset, persistence, and regression of neovascularization of the iris (NVI).¹¹⁴ In one study, the threshold for onset of NVI was 849 pg/ml similar to the dissociation constant for binding of VEGF to the VEGF1 receptor. The threshold for regression of NVI following PRP was lower, at 378 pg/ml, implying that the VEGF required to sustain established neovascularization is lower than that required to induce NVI.¹¹⁴

The blood–aqueous barrier (BAB) and the blood–retina barrier (BRB) are both disrupted by BRVO and CRVO. Using fluorophotometry, aqueous and posterior vitreous fluorescein concentrations were higher in eyes with BRVO and CRVO than in unaffected fellow eyes or of age-matched control eyes.¹¹⁷ Moreover, the degree of barrier breakdown was greater in CRVO than BRVO and greater in ischemic CRVO than nonischemic CRVO.¹¹⁷ All of these relationships are what one would expect if VEGF is the mediator of the BAB and BRB breakdown.

What Does the Response of RVO to Intravitreal Anti-VEGF Drugs Say About Pathophysiology?

An injection of intravitreal bevacizumab or ranibizumab can rapidly decrease the venous dilation, tortuosity, amount of intraretinal hemorrhage, and severity of macular edema. That is, the effect of anti-VEGF drugs goes beyond reversal of hyperpermeability suggesting that many of the multiple functions of VEGF are involved in producing the clinical picture of RVO. It has been hypothesized that thrombosis with ischemia upregulates VEGF locally, which secondarily causes endothelial hyperplasia within the already compromised venous lumen, endothelial adhesion of inflammatory cells, and NO mediated vasodilation.^{25,158} The injection of anti-VEGF drugs may counteract these effects, reverse VEGF-induced vasodilation and blood–retina barrier breakdown, and thus produce the observed improvement in venous distention and degree of intraretinal hemorrhage.

2.4 Retinal Neovascularization

In BRVO, retinal neovascularization typically occurs at the junction of nonperfused and perfused retina (Fig. 2.20). Nonperfused retina is associated with preretinal hypoxia in animal models of BRVO.⁷² The causes of this localized neovascularization, as opposed to the remote neovascularization of the iris seen more commonly in CRVO, are conjectural. There may be regional differences in upregulation of VEGF receptors causing a higher density at these junctional regions.¹¹³ In addition, increased concentrations of angiogenic lipid hydroperoxides may be present at nonperfused–perfused retinal borders.¹⁵⁹ VEGF can cause upregulation of bFGF, which acts synergistically with VEGF to induce angiogenesis.¹¹⁶ In contrast to BRVO, posterior segment neovascularization after CRVO is more likely to occur at the optic disc than in the retina.^{160,161} Anterior segment neovascularization is more common after CRVO than BRVO, presumably reflecting the lower levels of intraocular VEGF that occur in BRVO.¹⁶²

Retinal neovascularization after RVO is more likely to occur if the vitreous is attached to the retinal surface. Vitreous attachment may serve to increase concentrations of angiogenic cytokines locally and promote focal growth of new vessels.

The physical scaffold of vitreous fibrils may be another reason for the increased frequency of new vessel growth in such eyes.^{162,163}

Retinal and iris new vessels after RVO lack tight junctions.¹⁶⁴ The clinical correlate is leakage to fluorescein during fluorescein angiography, a characteristic differing from collateral vessels within the retina.

2.5 Pathogenetic Considerations Specific to Central Retinal Vein Occlusion

The clinically observed association of primary open-angle glaucoma and CRVO is undisputed. The following is a possible pathophysiologic basis. The optic disc forms a barrier between two pressure compartments – the intraocular pressure compartment anteriorly and the intracranial pressure compartment posteriorly.¹⁶⁴ Patients with primary open-angle glaucoma experience an increased pressure gradient across the optic disc. This may alter central retinal vein hemodynamics over long periods of time, produce endothelial changes, and increase central retinal venous resistance. The net effect of all of these conjectural changes could be an increased risk of thrombosis.¹⁶⁴

Spontaneous Venous Pulsations and CRVO

Spontaneous venous pulsations (SVP) are caused by variations in the pressure gradient in the lumen of the central retinal vein as it traverses the lamina cribrosa.¹⁷⁰ An increase in intracranial pressure or an increase in central venous resistance distal to the point of pulsation can stop SVP. The prevalence of SVP drops from 98% in normal elderly subjects to 54% in elderly patients with glaucoma.¹⁶⁴ In CRVO, the resistance in the CRVO distal to the lamina cribrosa rises, and SVP ceases. If a patient without full-fledged signs of CRVO has absence of SVP in the suspected eye but SVP in the fellow eye, CRVO should be considered as a diagnosis to explain the asymmetry.

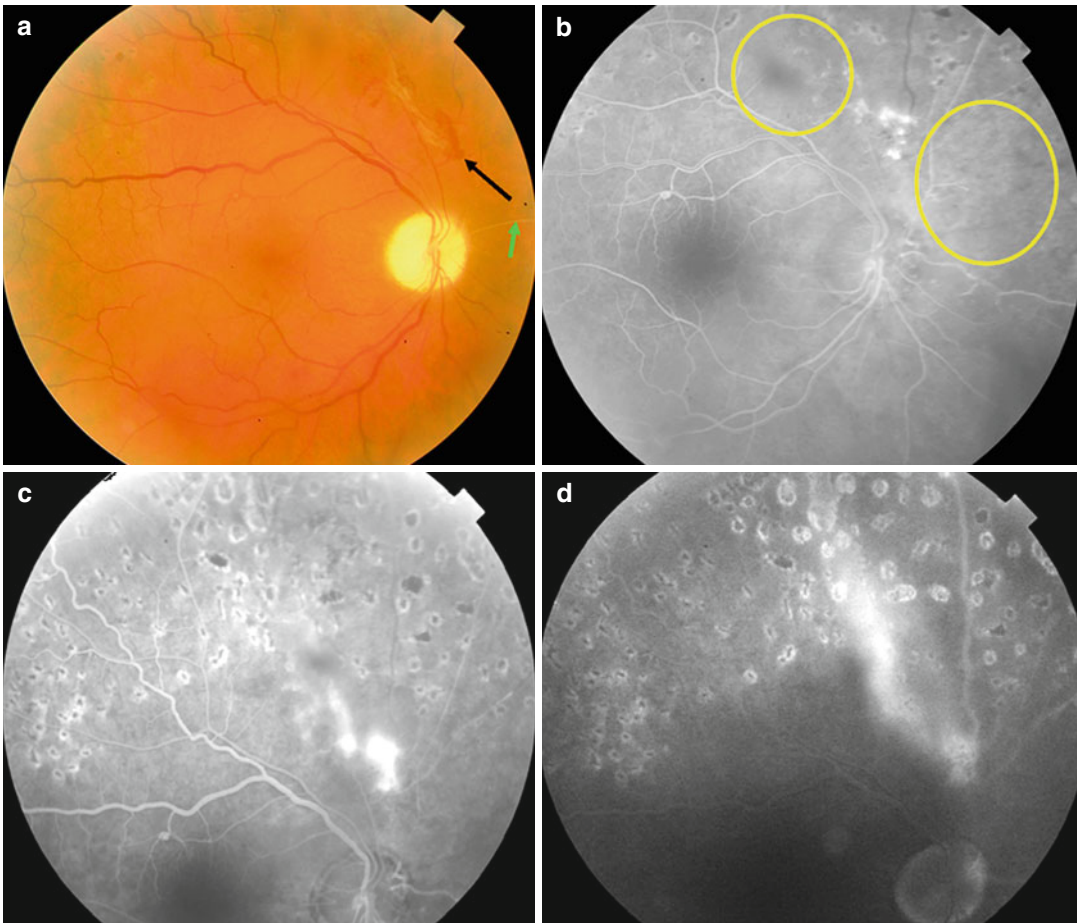


Fig. 2.20 Retinal images from a patient with BRVO and retinal neovascularization. (a) Color fundus photograph of the right eye showing retinal new vessels (*black arrow*) and a white, nonperfused vein (*green arrow*). (b) Frame from the early phase of the fluorescein angiogram showing the hyperfluorescent neovascularization at the border

of nonperfused retina (*yellow ovals*) and perfused retina. (c, d) Later frames of the fluorescein angiogram show leakage of fluorescein dye, shown as hyperfluorescent plumes emanating from the fronds, reflecting the abnormal degree of fenestration of new vessels

The pathophysiology of CRVO may be different in different subsets of patients, such as different age groups. Although abnormalities of the vessel wall seem to be the primary abnormality in the typical older patient, in the younger patient, an inflammatory basis has long been proposed instead, though without direct evidence.¹⁶⁵ In a minority of patients, the primary cause seems to be a thrombophilic state (see Chaps. 3 and 5).

The pathophysiologic basis for retinal hemorrhages in CRVO is widely understood, but manifestations of retinal whitening caused by ischemia and obstruction to the flow of axoplasm in the nerve fiber layer are less well recognized and understood.^{52,166,167} In the small percentage of patients with cilioretinal arteries who develop CRVO, a relative obstruction to blood flow occurs in the distribution of the cilioretinal artery (Fig. 2.21). In some cases, back-and-forth blood flow can be seen in the cilioretinal arteriole during the cardiac cycle. That flow implies that there is no focal blockage to the artery, but rather intravascular resistance posed by the head of pressure in the CRV against which the cilioretinal artery is pumping (Fig. 2.22).¹⁶⁸ In the diagram of hypoth-

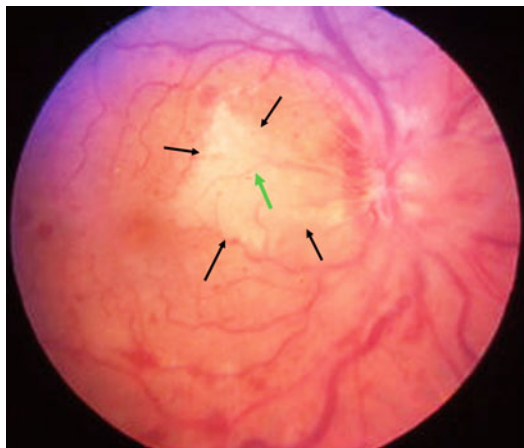


Fig. 2.21 Fundus photograph of a patient with a cilioretinal artery who developed a CRVO. The intravenous pressure of the CRV rose to a level sufficient to severely reduce the blood flow supplied to the part of the retina supplied by the cilioretinal artery. This ischemic area lost transparency and developed ischemic whitening (*black arrows*). The involved cilioretinal artery is denoted by the *green arrow*

esized intravascular pressure relationships in this situation, there is no driving force to move blood through the circulatory pathway fed by the

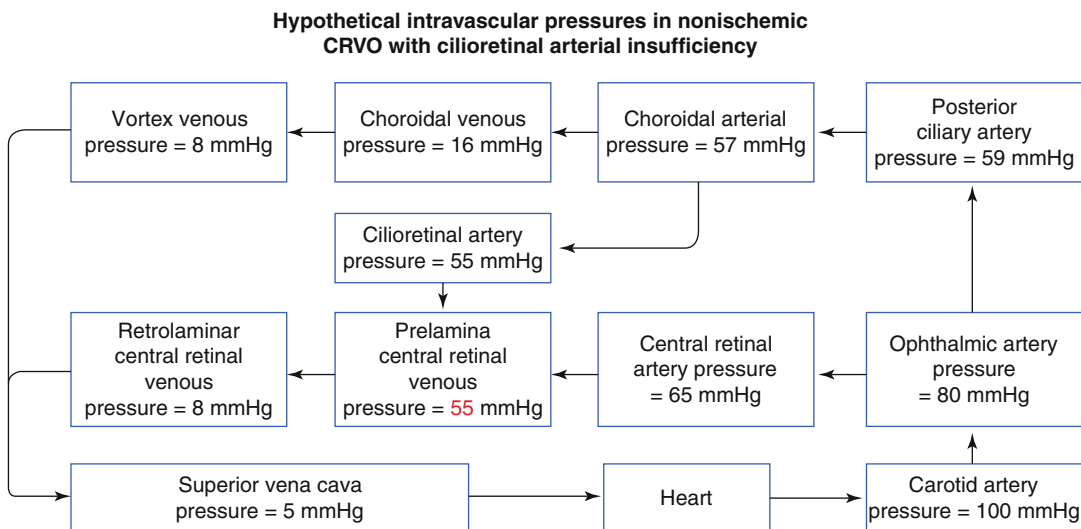


Fig. 2.22 Diagram of the hypothetical intravascular pressures found in a case of nonischemic CRVO with cilioretinal arteriolar insufficiency. Refer to Fig. 2.4b as the normal baseline in interpreting this diagram. The change is the elevation of the prelaminar central retinal venous pressure from 15 to 55 mmHg. This acute change, also

experienced by the retinal capillaries and arterioles upstream to the thrombus, acts as a hemodynamic block to perfusion by the cilioretinal artery which has a lower pressure than the central retinal artery. The retina served by the cilioretinal artery is therefore ischemic and loses its transparency

cilioretinal artery, which leads to a functional, but not anatomic, blockade of blood flow.

The degree of ischemia caused by the thrombus in CRVO depends on the percentage of the venous lumen occluded by the thrombus and the availability of collateral venous outflow. The latter consideration translates anatomically into the location of the thrombus relative to the lamina cribrosa. The more anterior the thrombus, the fewer the alternative pathways for drainage of venous blood, and the greater the ischemia for any given degree of luminal occlusion by the clot. The more posterior the thrombus, the greater the number of alternative pathways for drainage of venous blood and therefore less ischemia.³³

In hemodynamic terms, a higher degree of ischemia correlates with a higher prelaminar central venous pressure. An hypothetical example of intravascular pressure relationships in an ischemic CRVO is shown in Fig. 2.23. The driving pressure for blood flow across the retinovascular tree is only 3 mmHg because the venous intravascular pressure approaches the central retinal artery pressure. A low driving pressure results in sluggish retinal blood flow, higher oxygen extraction from the

blood than normal, and, if the retinal blood flow is reduced enough, ischemia. If thrombosis is severe enough and CRV pressure rises enough, not only can cilioretinal artery flow be impeded but also flow in branch retinal arterioles.¹⁶⁹ Retinal transparency is lost with the development of ischemic retinal whitening (Figs. 2.24, 2.25, and 4.5). It is not well appreciated, but true, that an ischemic CRVO may fail to show capillary nonperfusion early on. Capillary nonperfusion may take 3 weeks to develop. Loss of retinal transparency, poor visual acuity, and serous macular detachment – all present in the subject of Fig. 2.25 – point to the ischemic nature of the CRVO in the face of a relatively innocuous fluorescein angiogram.

2.6 Pathogenetic Considerations Specific to Branch Retinal Vein Occlusion

In acute BRVO, the arteriole to the involved sector transiently dilates and subsequently constricts secondary to a local decrease in NO.¹⁷¹ Secondary

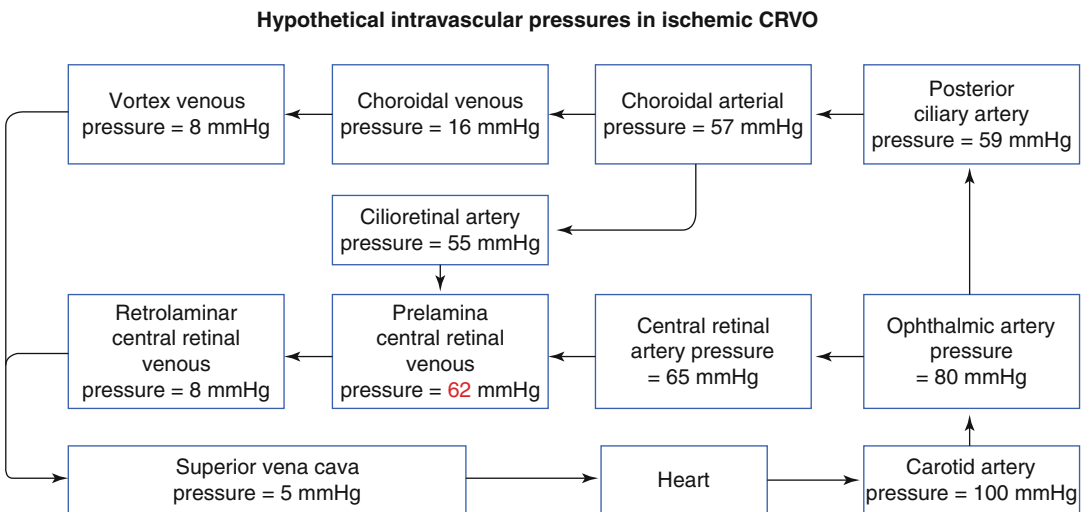


Fig. 2.23 Diagram of the hypothetical intravascular pressures found in a case of ischemic CRVO. Refer to Fig. 2.4b as the normal baseline in interpreting this diagram. The change is the elevation of the prelaminar central retinal venous pressure from 15 to 62 mmHg. This acute change, also experienced by the retinal capillaries and arterioles upstream to the thrombus, serves as a hemo-

dynamic block to perfusion by the cilioretinal artery, if one is present. It also reduces the perfusion pressure to the retinal tissue supplied by the central retinal artery. As we have posed the case, the perfusion pressure amounts to only 3 mmHg, and the sluggish perfusion may deliver so little oxygen to the retina that more widespread hypoxia is caused, with loss of retinal transparency

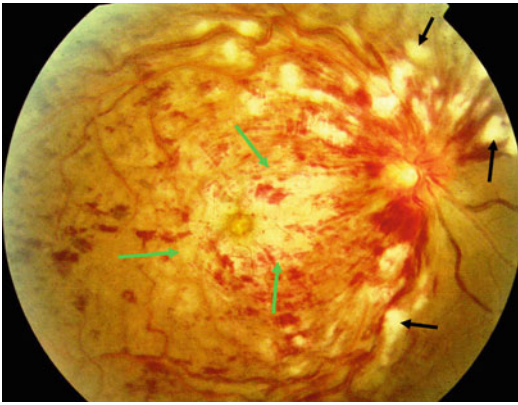


Fig. 2.24 Color fundus photograph of an ischemic CRVO. Cotton wool spots (*black arrows*) occur in the distribution of the radial peripapillary capillaries. Macular whitening (area bounded by *green arrows*) in an area supplied by the central retinal artery implies that the occlusion is severe and causing ischemia. The visual acuity was counting fingers. Other examples of this are shown in Figs. 2.25 and 4.6

arteriolar vasoconstriction is associated with subsequent capillary nonperfusion to the affected retina. Local injection of a NO donor, sodium nitropruside, can overcome this vasoconstriction.¹⁷¹

In a cat model of acute BRVO, 3H-thymidine labeling as an index of retinal vascular proliferation was found in the retina involved by the occlusion, but not in uninvolved retina. Endothelial uptake of thymidine was primarily venular, with some capillary uptake, but no arteriolar uptake.¹⁴¹ The clinical observation that retinal neovascularization after BRVO originates from venules is consonant with this experimental observation.¹⁴¹

Just as CRVO can occur in various grades of severity, with effects on perfusion and retinal transparency, the same is true with BRVO. A concept of arterial insufficiency has been developed based on back pressure by the obstructed vein.¹⁷² Branch retinal arterial filling to the involved sector of the retina is delayed.

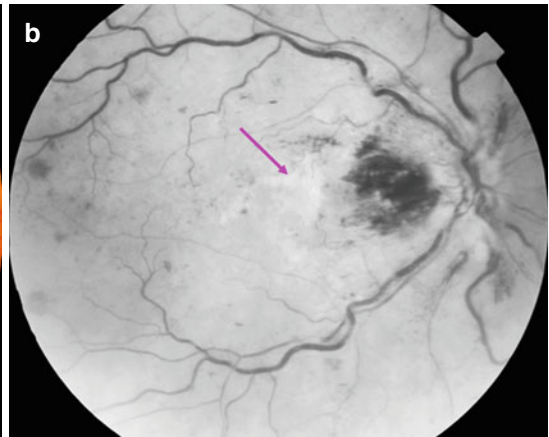


Fig. 2.25 Images of perimacular retinal whitening associated with an ischemic central retinal vein occlusion with extensive submacular fluid. (a) Color fundus photograph shows dilated veins, intraretinal hemorrhage and a perimacular, partial annulus of ischemic retinal whitening (*black arrow*). (b) Red-free photograph of the same eye. It may be easier to see the ischemic whitening (*purple arrow*) with red-free photography. (c) Scanning laser ophthalmoscopic fundus photograph of the same eye. Ischemic whitening is probably best visualized this way (*yellow arrow*). The OCT is decentered in this patient with poor central visual acuity, as shown by the nonfoveal location of the green crosshairs. (d) Radial line-scan OCT

image shows marked subretinal fluid and little intraretinal thickening. (e) ETDRS grid with mean subfield thicknesses. The central subfield thickness of 1,264 μ is composed primarily of subretinal fluid and does not reflect marked intrinsic retinal thickening. (f) Frame from the laminar venous phase of the fluorescein angiogram shows some irregularity of the border of the foveal avascular zone and slight enlargement in the foveal avascular zone diameter. (g) Frame from the late phase of the fluorescein angiogram showing fluorescein leakage from the posterior pole vessels and hyperfluorescence of the disc. This patient later developed anterior segment neovascularization and neovascular glaucoma

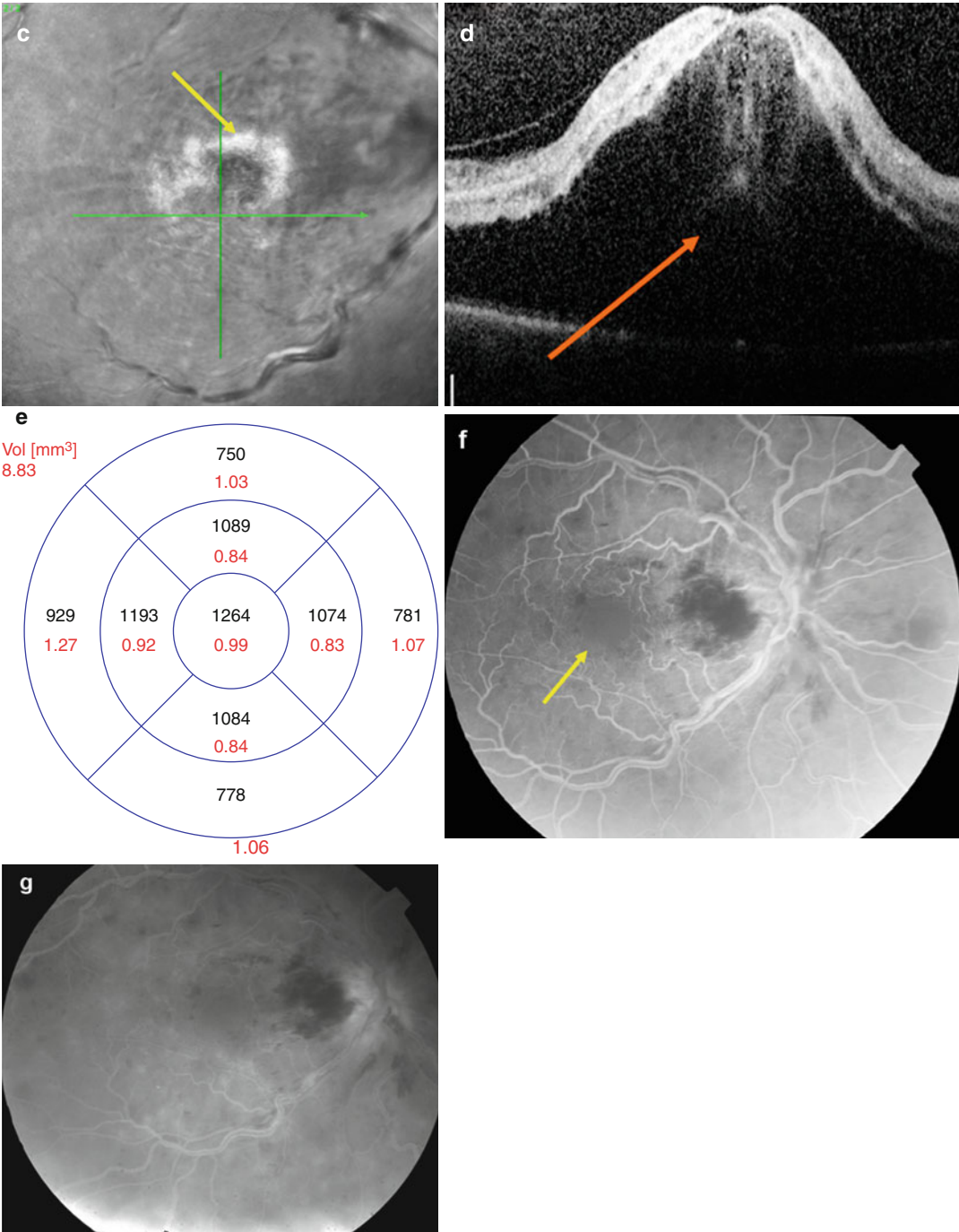


Fig. 2.25 (continued)

2.7 Animal Models of Retinal Vein Occlusion

2.7.1 Animal Models of BRVO

No animal model has been developed yet in which BRVO develops as an intrinsic part of systemic disease. All models involve intentional trauma designed to produce venous occlusion, usually by diathermy or laser.¹⁷³

A mouse model of BRVO and secondary retinal neovascularization was described in C57BL/6 mice using Rose Bengal infusion systemically followed by laser irradiation of the veins using light of wavelength 531 nm, power 50 mW, spot size 50 μ , and duration 3 s. Retinal neovascularization was reproducibly induced, and retinal mRNA expression of VEGF was demonstrated.¹⁷⁴ The use of Rose Bengal reduces the amount of laser energy required to produce a vein occlusion.¹⁷⁵

An analogous model of BRVO in the dog has been developed for studies designed to develop equipment for endovascular thrombolysis.¹⁷⁶ Histologic evidence of thrombolysis was achieved.¹⁷⁵

A miniature pig model of BRVO in which argon laser is used to occlude a temporal vascular venous branch has been described.⁶⁰ Miniature pigs lack a foveal avascular zone.⁶⁰ Unlike other animal models, the miniature pig model produces retinal neovascularization in some cases. Preretinal partial pressure of oxygen measurements with oxygen sensitive microelectrodes has shown that occluded zones are associated with preretinal hypoxia in this model of BRVO.⁷¹ Another pig model has used laser-induced branch venous occlusion assisted by photodynamic thrombosis with Rose Bengal.¹⁷⁷

A rhesus monkey model of BRVO in which retinal veins are occluded with argon laser produces changes that mimic human disease in the acute stage, but not in the chronic stage.^{173,178,179} It fails to capture the aged condition of the human who usually develops BRVO, but it has provided insights into pathophysiologic stages in the disease. In the acute phase from 1 to 6 h after the venous occlusion, the main observation is increased leakage

from the affected capillaries. The second stage occurs from 6 h to 1 week postocclusion during which time endothelial cells and pericytes degenerate. Exposed capillary basement membranes can induce microthrombi leading to progressive capillary nonperfusion. The third stage occurs 1–5 weeks after the occlusion, when acellular channels are left composed of basement membrane.

No microaneurysms were found in this model, presumably because the animals had healthy vascular systems at the time of the induced occlusions.^{173,178,180} Moreover, the model fails to exhibit persistent retinal edema or preretinal neovascularization, although intraretinal neovascularization was seen in ischemic cases.¹⁷³ In humans, based on serial measurements of the foveal avascular zone in BRVO, there is evidence that capillary closure is irreversible by 3 months after the acute occlusion.¹⁸¹ A similar monkey model of laser-induced BRVO has also been used to study retinal pO_2 after BRVO and under the influence of systemic hyperoxia.⁶⁸

Sites of VEGF production in ischemia vary in different species. In rats and cats, VEGF is produced by astrocytes and Muller cells in response to physiologic hypoxia. In mice, a model of retinopathy of prematurity has shown localization of VEGF production in the Muller cells. In a simian model, however, VEGF occurs in ganglion cells and cells of the inner nuclear layer.¹⁰⁵ Species differences preclude exact extrapolation of the model observations to human disease, but these models offer clues regarding some aspects of common sequelae.

2.7.2 Animal Models of CRVO

A rabbit model has been developed that is intended to simulate the panretinal effects of CRVO.¹⁸² In the rabbit, there is no CRV, and all veins are located above the retina rather than within it. In the model, all major retinal veins were occluded by injecting Rose Bengal dye followed by argon-laser photocoagulation of the veins at the optic disc margin.^{183–185} In this model, arterial flow stopped with accompanying retinal

whitening. Recanalization of the occluded veins and clearing of retinal hemorrhages occurred more rapidly than in human disease.¹⁸² Retinal atrophy on OCT following this ischemic model of CRVO was demonstrated.¹⁸²

In a variation of this idea, a monkey model of iris neovascularization has been developed in which laser occlusion of all four major branch retinal veins reproducibly leads to iris neovascularization.^{108,118} A different monkey model has been developed in which repetitive intravitreal injections of VEGF caused capillary leakage, microaneurysm formation, and capillary nonperfusion.^{41,176} Cynomolgus monkey VEGF DNA sequences are 99% identical to human VEGF sequences, and the nucleotide changes are conservative. This means that the VEGF in simian models is identical to human VEGF and can be blocked by monoclonal antibodies raised against human VEGF.¹⁰⁵ Such injections prevented development of iris neovascularization.

2.8 Summary of Key Points

- Thrombosis is the result of opposing biochemical pathways mediating coagulation and fibrinolysis.
- The viscosity of blood is primarily determined by the hematocrit. Hemodilution is a modestly effective treatment for RVOs.
- The driving force for blood flow through the retinal vessels is the ocular perfusion pressure.
- Under normal conditions, the prelaminar central retinal venous pressure is approximately equal to the intraocular pressure.
- The uveal venous pressure is approximately 1 mmHg higher than the intraocular pressure.
- Block diagrams showing measured and hypothetical intravascular pressures at various locations around the ocular vascular circuit help to understand the clinical profiles of RVO.
- Laplace's law is used for deducing that the choroidal capillary pressure is higher than the retinal capillary pressure.
- Poiseuille's law is used for understanding how retinal arterial constriction after focal laser treatment reduces the driving force for macular edema.
- Experimental models suggest that the lumen of the CRV must be occluded $\geq 90\%$ before any clinical signs of CRVO develop.
- The more anterior the postlaminar thrombus in CRVO, the more ischemic the occlusion because there are fewer collaterals available to bypass the thrombus.
- Retinal blood flow is one-tenth of choroidal blood flow. The oxygen extraction from the retinal blood is much higher than the oxygen extraction from the choroidal blood.
- There are oxygen gradients within the retina. The oxygen tension is highest adjacent to retinal arteries and lowest adjacent to retinal veins. The midretinal cell layers have a lower oxygen tension than the outer and inner layers.
- Retinal vessels change their radius in response to nitric oxide and other signaling molecules that vary in concentration according to local oxygen tension (autoregulation).
- Retinal transparency is an indicator of retinal oxygenation. Retinal whitening accompanies ischemia.
- Starling's law explains the driving force for macular edema formation after RVO.
- Vascular endothelial growth factor and other cytokines regulate vascular permeability and angiogenesis after RVO.
- Animal models provide helpful clues regarding the pathogenesis of RVOs, but species differences limit generalizations from the models.

2.9 Future Directions

It is possible to stumble upon effective treatment for RVO and sequelae. An example would be grid laser for macular edema secondary to BRVO in which a treatment pioneered for diabetic retinopathy was empirically tried and found to be modestly, but beneficially effective. After the fact, a physiologic basis for its effectiveness was hypothesized and tested. We think that we now understand how it works. A more rational and efficient approach is to develop a detailed understanding of pathophysiology first and then develop treatments that address specific steps in the pathways that lead to the disease. The discovery of VEGF, its effects on the retina in model systems, and subsequent creation

of antibodies to block its effects in RVO and other diseases exemplify the latter approach. Efforts to understand retinal hemodynamics in greater detail with actual measurements of pressures in locations presently inaccessible are likely to further our understanding. The molecular basis of thrombosis, fibrinolysis, vasopermeability, angiogenesis, and autoregulation will likely be further defined, as well as the interactions and feedback loops that connect the pathways.

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