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Animal Models of Retinal Vein Occlusion

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Purpose. To provide a comprehensive and current review on the available experimental animal models of retinal vein occlusion (RVO) and to identify their strengths and limitations with the purpose of helping researchers to plan preclinical studies on RVO.

Methods. A systematic review of the literature on experimental animal models of RVO was undertaken. Medline, SCOPUS, and Web of Science databases were searched. Studies published between January 1, 1965, and March 31, 2017, and that met the inclusion criteria were reviewed. The data extracted included animal species used, methods of inducing RVO, and the clinical and histopathologic features of the models, especially in relation to strengths, limitations, and faithfulness to clinical sequelae.

Results. A total of 128 articles fulfilling the inclusion criteria were included. Several species were used to model human branch and central RVO (BRVO; CRVO) with nonhuman primates being the most common, followed by rodents and pigs. BRVO and CRVO were most commonly induced by laser photocoagulation and all models showed early features of clinical disease, including retinal hemorrhages and retinal edema. These features made many of the models adequate for studying the acute phase of BRVO and CRVO, although macular edema, retinal ischemia, and neovascular complications were observed in only a few experimental animal models (laser-induced model in rodents, pigs, and nonhuman primates, diathermy-induced model in pigs, and following intravitreal injection of PD0325901 in rabbits for BRVO; and in the laser-induced model in rodents, rabbits, and nonhuman primates, diathermy-induced model in nonhuman primates, following permanent ligation of the central retinal vein in nonhuman primates, and with intravitreal injection of thrombin in rabbits for CRVO).

Conclusions. Experimental animal models of RVO are available to study the pathogenesis of this disease and to evaluate diagnostic/prognostic biomarkers and to develop new therapeutics. Data available suggest laser-induced RVO in pigs and rodents to be overall the best models of BRVO and the laser-induced RVO rodents the best model for CRVO.

Keywords: retinal vein occlusion, retinal vein thrombosis, ischemia, experimental models, animal models, in vivo models

Retinal vein occlusion (RVO) is the second most common vascular cause of visual loss, surpassed only by diabetic retinopathy.[1–5] Obstruction of the retinal venous system is commonly caused by thrombus formation, which may result in devastating consequences, including macular edema and neovascular complications, leading to visual impairment and blindness.[1,6–14] RVO has been typically classified into central (CRVO), branch (BRVO), hemicentral and hemispheric types based on the site of the occlusion.[1,2,4,5,15–17] Each of these RVO types has been further subclassified into ischemic and nonischemic forms based on the severity of the disease and the likelihood of developing neovascular complications. Ischemic RVO (iRVO) is the most severe form, associated with higher risk of complications and having a poorer prognosis than non-iRVO.[1,2,4,15,17,18]

Current treatments of RVO, including laser photocoagulation, intravitreal anti-VEGF therapies, intravitreal steroids, and pars plana vitrectomy, target the complications of RVO, namely macular edema and neovascularization and its consequences,[1,5,7,16,17,19–24] and may not fully reverse the functional and structural damage result of the disease.[10,25–59] Furthermore, each of these treatments carries a risk to patients, such as destruction of the retina following laser photocoagulation, endophthalmitis following intravitreal injections, and cataract and glaucoma as a result of steroid administration. Treatments for macular edema that are a result of RVO have been predominantly investigated for the nonischemic form, with most randomized clinical trials excluding or including only few with the iRVO.[35,39,40,45,47,52–55,60] In trials in which they have been included, only approximately 50% or less of patients with iRVO show a meaningful improvement in visual acuity following these therapies,[34,37,38,45,48–51,57] with often poor final visual acuity ($\leq$ 20/100) despite treatment.[10,34,36–38,41,43,51,57]

Further research is still needed to improve current understanding of the pathogenesis of RVO as well as to identify more clinically effective and cost-effective therapeutic options. This is especially true for patients with iRVO.

Experimental animal models often can be useful to study disease mechanisms and to test the efficacy and potential

toxicity of new treatments. Such animal approaches have been successful in ophthalmic research, allowing advancement in our understanding of pathogenesis and development of improved novel therapies.[61–66] Experimental animal models of RVO also are available, which variably develop functional and structural features resembling those present in people with this disorder. Herein, we aim at providing a comprehensive up-to-date review on experimental animal models of RVO including species, methods of vessel occlusion, their clinicohistopathologic features, and the limits of their translational value. Taken together, this focused and in-depth review ought to help researchers design future studies and appreciate the strengths and weaknesses of the animal models they use.

Methods

A systematic review of the literature was conducted, and data sources were Medline, SCOPUS, and Web of Science databases. Keywords including "retinal vein occlusion," "retinal vein thrombosis," and "retinal vein obstruction" were combined with "experimental models" or "animal models." The search covered published articles from January 1, 1965, to March 31, 2017, and was filtered to include articles in English only. The included articles of studies describing methods of creating animal models of RVO and their findings were analyzed, and data contained in these articles were used to inform species-specific model systems, the range of methods for inducing vein occlusion, pathologic and clinical features developed in these models, and strengths and limitations of available models. The information extracted was used to populate Tables 1 through 8 of this review. In addition, their clinical value and potential translational implications for the management of patients with this disorder was considered. Changes on levels of cytokines/chemokines/growth factors and other biochemical and molecular events occurring as a result of the induction or RVO in these models, as well as effects of treatments tested in these animal models are beyond the scope of this review and, thus, are not summarized herein.

Results

Studies Included

After removal of duplicates, a total of 320 titles were identified and their abstracts obtained and evaluated for potential inclusion in the review. Of the 320 abstracts, 193 were found to relate to studies outside the scope of this review and, thus, were excluded. Full articles of the remaining 128 studies were obtained, found to be directly related to the topic of this review, and used to extract pertinent data.

Species

Several animal species have been used to study RVO, including rodents,[67–100] rabbits,[101–114] cats,[115–124] dogs,[125–127] pigs,[128–156] and nonhuman primates[82,111,129,157–196] (Tables 1, 2). Each of these species has its own size and anatomic advantages, but also ethical challenges and cost implications; these have been summarized in Table 3. Although the retina and retinal vessels of these animals share many anatomic features with humans, differences still exist and are more pronounced in some species (Table 4). None of the animal models, with the exception of the nonhuman primate, have an anatomic macula or fovea centralis.[197] Pigs,[198–202] cats,[201,203] and dogs[198,204] have a central retinal area with high density of ganglion cells and cone photoreceptors known as area centralis, which would correspond to the fovea centralis in humans but is less specialized and cannot be identified by gross fundus examina-

Table 1. Animal Species and Techniques Used to Induce BRVO

Species	Laser Photocoagulation ± Photosensitizer, *n*	Photodynamic Therapy + Photosensitizer, *n*	Diathermy, *n*	Intravitreal PD0325901, *n*	Total, *n*	References
Rodents, *n*	17	3	0	0	20	70, 74, 80, 83–86, 88–100, 220
	(ischemia = 8)				**(ischemia = 8)**	**80, 83, 85, 89, 90, 92, 96, 97**
Rabbits, *n*	6	1	0	1	9	104–107, 109, 110, 112, 114
				(ischemia = 1)	**(ischemia = 1)**	**114**
Cats, *n*	4	1	5	0	10	115–124
Dogs, *n*	3	0	0	0	3	125–127
Pigs, *n*	20	2	4	0	26	129–134, 136–142, 144–156
	(ischemia = 6)				**(ischemia = 6)**	**130–134, 154**
Nonhuman primates, *n*	21	0	0	0	21	129, 175–181, 183–194, 196
	(ischemia = 13)				**(ischemia = 13)**	**175, 176, 178–181, 184, 187–190, 192, 193**
	(MO = 4)				**(MO = 4)**	**180, 186, 190, 193**
Total, *n*	71	7	9	1	89	

Bolded values represent models that addressed macular edema or ischemic features. Ischemia defined by one or more of the following criteria: development of neovascularization, extensive areas of retinal capillary nonperfusion, or areas capillary nonperfusion associated with atrophy/cell loss of the inner retinal layers (± outer retinal layers). MO, macular edema; *n*, number of articles.

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TABLE 2. Animal Species and Techniques Used to Induce CRVO

Species	Laser Photocoagulation ± Photosensitizer, *n*	Diathermy, *n*	Permanent Ligation of the Central Retinal Vein, *n*	Transient Ligation of the Optic Nerve, *n*	Intravitreal NPe6, *n*	Intravitreal Thrombin, *n*	Intravitreal ET-1, *n*	Total, *n*	References
Rodents, *n*	9	0	0	6	0	0	0	15	68–79, 220
	(ischemia = 4)							**(ischemia = 4)**	**68, 69, 74, 220**
Rabbits, *n*	1	0	0	0	1	1	1	4	101–103, 113
	(ischemia = 1)		**(ischemia = 1)**			**(ischemia = 2)**		**101, 102**	
Cats, *n*	0	0	0	0	0	0	0	0	
Dogs, *n*	0	0	0	0	0	0	0	0	
Pigs, *n*	0	0	0	1	0	0	0	1	128
Nonhuman primates, *n*	12	6	1	0	0	0	0	19	111, 157–174
	(ischemia = 9)		**(ischemia = 1)**					**(ischemia = 10)**	**157–160, 162–166, 174**
		(MO = 2)						**(MO = 2)**	**170, 171**
Total, *n*	22	6	1	7	1	1	1	38	

Bolded values represent models that addressed macular edema or ischemic features. Ischemia defined by one or more of the following criteria: development of neovascularization, extensive areas of retinal capillary nonperfusion, or areas of capillary nonperfusion associated with atrophy/cell loss of the inner retinal layers (± outer retinal layers). *n*, number of articles.

tion.[198,204] Unlike primates, the posterior segment of eyes of cats[205–208] and dogs[207–209]contains a reflective tapetum layer, which serves to intensify vision in dim light, and may affect the functional results when compared with humans.[205–208] With the exception of the rabbit, all above-mentioned animals, like humans, have a holangiotic retinal vasculature (i.e., vessels emerge from the optic disc and ramify, distributing over the entire retina).[210–213] Rabbits, in contrast, have a merangiotic retinal vascular pattern (i.e., vessels are not distributed all over the retina), by which the main temporal and nasal retinal vessels extend horizontally from the optic disc to the sides, giving smaller branches to form two wing-shaped vascularized areas and leave the rest of the retina avascular.[211,214,215] Some animals, namely pigs,[212,213] dogs,[210] and cats,[211] do not have a single central retinal artery; instead, they have multiple retinal arteries entering the retina at the margin of the optic disc. Furthermore, cats do not have a single central retinal vein but multiple veins instead.[211] Unlike humans and other species that normally have relatively straight retinal vessels (i.e., nontortuous), retinal vessels of dogs normally have various degrees of tortuosity.[210] Pigs are similar to humans in that they have an intraretinal arrangement of retinal capillaries,[212] as well as comparable scleral thickness, which makes them ideal for transscleral surgical or drug-delivery approaches.[200]

Generally, of all species used, nonhuman primates were found to have the closest ocular anatomy to the human eye,[210] followed by pigs. Unsurprisingly, this makes them superior choices to most other species, especially when considering only their retina and retinal vessel anatomy.

Methods of Inducing RVO

Several techniques have been used to induce an RVO in experimental animals. These have been summarized, including their advantages and disadvantages, in Table 5. In most cases, experimental RVO has been induced by traumatizing one or more retinal veins using laser photocoagulation.[67–75,80–92,96,97,101,104–111,115–118,125–127,129–147,156–167,174,176–194,216]

Branch Retinal Vein Occlusion. Experimentally, BRVO has been produced by using laser photocoagulation,[70,80,89,96,97,100,105,127,132,142,146,156,176,178,181,216] photodynamic coagulation,[93–95,112,119,148,149] diathermic cauterization,[75,120–124,150–152] or intravitreal injection of PD032590.[114]

Laser Photocoagulation. In this method, laser irradiation is performed on selected retinal veins to produce BRVO.[70,80,89,96,97,100,105,127,132,142,146,156,176,178,181,216] Classically, burns are placed approximately 0.5 to 2.0 disc areas from the optic disc, avoiding damage to the retinal arteries.[69,70,74,80,81,92,97,99,117,186,217] Laser photocoagulation is typically done on the slit-lamp using a contact lens.[68–72,74,81–83,86,88–92,97,99,100,104,108,117,126,132,134,135,137,139,141,186,187,192–194,196] Some studies have combined laser photocoagulation with vitrectomy.[147,176–178] Different types of laser and wavelengths have been used, commonly 514-nm Argon, and their parameters varied depending on the type of laser used, type of animal, and use or not of adjuvants (Table 6). Photosensitizers, such as Rose Bengal,[67–70,73,81,89,96,99–101,104,106,107,109,110,126,127,132,134,135,137,139,141,143,146,147,217] erythrosin B,[74] sodium fluorescein,[71,83,85,86,88,97,142,175,187,190–194,218] chloroaluminium sulfonated phthalocyanine,[105] PAD-S31,[186] and mono-L-aspartyl chlorin e6 (NPe6)[82] have been commonly used with the laser photocoagulation to minimize the amount of the laser energy required to produce the RVO. Rose Bengal has been the most commonly used photosensitizer,[67–70,73,81,89,96,99–101,104,106,107,109,110,126,127,132,134,135,137,139,141,143,146,147,217] whereby the dye is infused systemically (10–50 mg/kg) and the retinal vessels are exposed to highly focused laser irradiation.[67–70,73,81,89,96,99,101,104,106,107,109,110,126,127,132,134,135,137,139,141,143,146,147,217] Combination of intravitreal injec-

Table 3. Advantages and Inconveniences of Species Used as Animal Models of RVO

Animal	Advantages	Disadvantages
Rodents	• Low cost • Easy to obtain • Easy to handle • Reproducible • Feasible for genetic manipulation • Suitable for evaluating the effects of therapeutic interventions • Small size of the animal, which allows keeping larger number of animals in smaller spaces • Share some anatomic similarities with human (Table 4)	• Small eyes • Lack of macula
Rabbits	• Low cost • Easy to obtain • Relatively large eyes • Accessible retinal vessels • Eye very suitable for diagnostic and surgical procedures	• Anatomy of the rabbit's retina significantly different from that of humans • Lack of macula
Cats	• Relatively large eyes • Accessible retinal vessels • Eye very suitable for diagnostic and surgical procedures • Share some anatomic similarities with human (Table 4)	• High cost • Limited availability • Can be aggressive and difficult to handle • Ethical considerations • Larger spaces required to maintain them • Lack of macula • Requires large housing facilities
Dogs	• Relatively large eyes • Accessible retinal vessels • Eye suitable for diagnostic and surgical procedures • Share some anatomic similarities with human (Table 4)	• High cost • Limited availability • Can be aggressive and difficult to handle • Ethical considerations • Lack of macula • Requires large housing facilities
Pigs	• Eye size and scleral thickness are nearly identical to humans • Eye suitable for diagnostic and surgical procedures • Share some anatomic similarities with human (Table 4)	• High cost • Large size of the animal • Requires large housing facilities • Lack of macula
Nonhuman primates	• Anatomy almost identical to human • Accessible retinal vessels	• High cost • Limited availability • Difficult to handle • Requires highly experienced team, and special housing facilities • Ethical considerations

tion of thrombin (50 units) and laser photocoagulation has also been reported. Endophotocoagulation has also been used to achieve a vein occlusion; for this technique, an endolaser probe is inserted into the eye through a sclerostomy (without removing the vitreous) and retinal veins are then photocoagulated until evidence of occlusion is seen.[146,147]

Photodynamic Therapy. Photodynamic coagulation is another method that has been used to induce BRVO.[93–95,112,119,148,149] This method involves light illumination using a slit-lamp and a contact lens, or an endo illuminator in combination with vitrectomy aiming at selected retinal vein or veins, with care not to damage retinal arteries, for a duration ranging between 6 and 20 minutes until evidence of venous occlusion is observed.[93–95,112,119,148,149] Photosensitizers, such as Rose Bengal,[93–95,112,119,148,149] sodium fluorescein,[119] and NPe6,[82] have been used in different doses depending on the species used to facilitate thrombus formation.

Diathermic Cauterization. An alternative way to produce experimental BRVO is by using diathermy, which has been undertaken via a pars plana sclerotomy.[75,120–124,150–152] In cats, BRVO has been induced with indirect ophthalmoscopy and 20-gauge bipolar diathermy that is applied to the targeted vein/veins for 5 seconds.[120–124] In pigs, a technique has been described that produces a BRVO following a temporal canthotomy, conjunctival incision, and performance of three sclerotomies at 10, 2, and 5 o'clock, 2 mm posterior to the corneal limbus.[150–153] In this method, a light source and a blunt bipolar diathermy probe are inserted into the vitreous and one or two major retinal veins are coagulated approximately 1 disc diameter away from the optic disc for 5 to 7 seconds after 5 seconds of compression and under direct view

Table 4. Similarities and Differences of Retina and Retinal Vasculature of the Different Animal Species Used in RVO Studies

	Rodents	Rabbits	Cats	Dogs	Pigs	Nonhuman primates	Humans	References
Anatomic macula and fovea centralis	Absent	Absent	Absent	Absent	Absent	**Present**	**Present**	197–204
Tapetum layer	**Absent**	**Absent**	Present	Present	**Absent**	**Absent**	**Absent**	205–209
Vascular pattern	**Holangiotic**	Merangiotic	**Holangiotic**	**Holangiotic**	**Holangiotic**	**Holangiotic**	**Holangiotic**	210–215
Central retinal vein	**Single**	**Single**	Multiple	**Single**	**Single**	**Single**	**Single**	210–213
Central retinal artery	**Single**	**Single**	Multiple	Multiple	Multiple	**Single**	**Single**	210–213
Major arterial and venous branches, *n*	5–7	2	3	Multiple	**3–4**	**4**	**4**	210–215

Bold text indicates as in humans.

through an operating microscope and with the aid of a fundus contact lens.[150–153] This procedure does not involve vitrectomy.[150–153]

Intravitreal Injection of Substances. PD0325901 (N-[2,3-dihyroxy-propoxy]-3,4-difluoro-2-[fluoro-4-iodo-phenylamino]-benzamide) is a mitogen-activated protein kinase inhibitor that has been used in clinical trials for the treatment of solid tumors and has been found to be associated with development of BRVO. Based on this, one study established a rabbit model of BRVO by a single intravitreal injection of PD0325901 (0.5 or 1.0 mg per eye) using a 27-gauge needle inserted approximately 3 mm posterior to the limbus at the superior temporal quadrant and advanced until into the midvitreous cavity.[114]

Central Retinal Vein Occlusion. CRVO has been produced by laser photocoagulation,[67–75,101,111,157–167] diathermic cauterization,[168–170,172,195] permanent ligation of the central retinal vein,[174] transient clamping/ligation of the optic nerve,[76–79] or intravitreal injection of thrombin,[102,219] NPe6,[103] or endothelin-1 (ET-1).[113]

Laser Photocoagulation. In this method, all major branches are irradiated with laser to produce CRVO,[67–75,101,111,142,157–167] classically 0.5 to 2.0 disc areas from the optic disc, avoiding damaging the retinal arteries.[69,70,74,80,81,92,97,99,117,186,217] Similar to BRVO, laser photocoagulation is typically done on the slit-lamp using a contact lens.[68–72,74,81–83,86,88–92,97,99,104,108,117,126,132,134,135,137,139,141,186,187,192–194,196] with or without vitrectomy.[147,176–178] Different types of laser, wavelengths, and photosensitizers have been used.[67–71,73,74,81,83,85,86,88,89,96,97,99,101,104–107,109,110,126,127,132,134,135,137,139,141–143,146,147,166,175,186,187,190–194,217,218,220] In one study, a through-and-through suture was placed in the cornea, in addition to the laser photocoagulation in nonhuman primate models, to create an aqueous leak and subsequent hypotony to produce iris neovascularization.[166]

Diathermic Cauterization. Diathermic cauterization of the central retinal vein has been achieved through a lateral orbitotomy approach in nonhuman primates to produce CRVO.[168–170,172,195] In this method, diathermy is applied at the central retinal vein on the inferiomedial aspect of the optic nerve as it exits the optic nerve sheath, avoiding injury to the ciliary vessels.[168–170,172,195]

Mechanical Ligation.

- Permanent ligation of central retinal vein: Mechanical ligation of the central retinal vein was used in nonhuman primates to produce CRVO in one study.[174] Through a lateral orbital approach and using the operating microscope to aid visualization and achieve adequate magnification, the central retinal vein was identified and ligated using an 8–0 silk suture. Two approaches were then used to achieve a CRVO: (1) a small incision was made proximal to the suture and neoprene was introduced through a cannula into the central retinal vein where it solidified, or (2) the central retinal vein was cut after ligation.[174]
- Transient ligation or clamping of the optic nerve: Transient ligation/clamping (60–120 minutes) of the optic nerve using a lateral orbital approach has been used also to produce CRVO in rats and in pigs.[76–79] This method, however, included the ciliary vessels and the central retinal artery and, thus, not reproducing an isolated CRVO.

Intravitreal Injection of Substances.

- Thrombin: A different CRVO model, the Hirosaki model, was developed in rabbits as described in one study.[102] Based on the premise that the extrinsic coagulation mechanism can be triggered by thromboplastin in the perivascular connective tissues, CRVO was successfully created through the intravitreal injection of thrombin over the wall of the rabbit's retinal veins (thrombin solution 0.01 mL [5 units]) under direct vision using a 27-gauge needle. A Goldmann contact lens and operational microscope were used to view the fundus.[102]
- NPe6: Another animal model of CRVO, also in rabbits, described in one study, involved an intravitreal injection of a hydrophilic photosensitizer, mono-L-aspartyl chlorin e6 (NPe6) (50 and 100 μg). In this model, there was no direct exposure to a light source, instead the animals were naturally exposed to the daily light-dark cycle. The injection was performed approximately 2 to 3 mm posterior to the limbus using a 30-gauge needle and a 1-mL syringe.[103] In this particular model, CRVO, central retinal artery occlusion, and various degrees of vitreous hemorrhage developed after 1 week following injection.[103]
- ET-1: ET-1 is a peptide with vasoconstrictive properties normally produced by vascular endothelial cells.[113] Intravitreal injection of 1000 pmol of ET-1 solution over the disc, as observed by ophthalmoscope, using a 29-gauge needle and a 1-mL syringe was used to induce CRVO in rabbits in one study.[113] In this model, the occlusion lasted only 50 to 70 minutes.[113]

Clinical and Histopathologic Features of RVO Models

Clinical and/or histopathologic features observed in animal models of BRVO and CRVO were described in 89 and 38 articles, respectively, identified in our search. Macular edema has been addressed in only 4 of 21 studies on nonhuman primate models of BRVO, all laser-induced[180,186,190,193] and in only 2 of 21 studies in nonhuman primate models of CRVO,

Table 5. Advantages and Disadvantages of the Different Methods Used to Induce RVO

Method	Advantages	Disadvantages	References
Laser photocoagulation ± photosensitive dye	• Can be used to produce both CRVO and BRVO • Easy to undertake • Successful in 89%–100% of cases • Many studies supporting this technique	• Potential phototoxicity with photosensitizers and sun/light exposure • Inner retina damage at the site of the laser treatment • May rupture retinal vessels and cause vitreous hemorrhage • Requires laser equipment	68–70, 74, 75, 80, 83–86, 88–92, 96–99, 101, 104–107, 109–111, 125–127, 129–134, 136–142, 144–147, 150–160, 162–167, 175, 176, 178–181, 184, 187–190, 192, 193, 220
Photodynamic therapy + photosensitive dye	• Produces BRVO • Successful in 50%–100% of cases	• Potential phototoxicity with photosensitizers and sun/light exposure • Inner/outer retinal damage at the site of the light application • Exudative retinal detachment • Retinal necrosis • Requires specialized equipment	93–95, 112, 119, 148, 149
Diathermic cauterization	• Produces CRVO and BRVO • Successful in 90%–100% of cases	• Invasive • Requires access to surgical facilities to produce CRVO	120–124, 150–153, 168–170, 172, 173, 195
Permanent ligation of the central retinal vein	• Produces CRVO • Successful in 100% of cases	• Invasive • Requires access to surgical facilities to produce CRVO • May affect ciliary vessels and central retinal artery • Only 1 reported study	174
Transient ligation/clamping of optic nerve	• Produces CRVO • Successful in 100% of cases	• Invasive • Requires access to surgical facilities to produce CRVO • Affects ciliary vessels and central retinal artery	76–79, 128
Intravitreal thrombin injection	• Produces CRVO • No mechanical vascular damage	• Successful in only 43% of cases • Only 1 reported study	102
Intravitreal ET-1 injection	• Produces BRVO • Successful in 100% of cases • No mechanical vascular damage	• Only 1 reported study • Transient occlusion (50–70 minutes) • Affects both retinal arteries and veins	113
Intravitreal NPe6 injection	• Produces BRVO • Successful in 100% of cases • No mechanical vascular damage	• Only 1 reported study • May produce features unrelated to RVO	103
Intravitreal PD0325901 injection	• Produces BRVO • Successful in 100% of cases • No mechanical vascular damage	• Only 1 reported study • May produce features unrelated to RVO • Takes 1 week to produce RVO	114

BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; RVO, retinal vein occlusion; ET-1, endothelin-1; NPe6, mono-L-aspartyl chlorin e6.

both diathermy-induced.[170,195] Ischemia, defined by development of neovascular complications, extensive areas of capillary nonperfusion (capillary dropout), or both, or capillary nonperfusion associated with atrophy/cell loss of the inner retinal layers, has been reported in 28 of 89 studies in laser-induced BRVO models of rodents ($n = 8$),[80,83,85,89,90,92,96,97] pigs ($n = 6$),[130–134,154] and nonhuman primates ($n = 13$)[175,176,178–181,184,187–190,192,193]; PD0325901-induced BRVO models of rabbits ($n = 1$) [114]; and in 16 of 38 studies in laser-induced CRVO models in rodents ($n = 4$),[67–69,74] rabbits ($n = 1$),[101] and nonhuman primates ($n = 9$),[157–160,162–166] in permanent ligation of central retinal vein CRVO models in nonhuman primates ($n = 1$),[174] and in thrombin-induced CRVO models in rabbits ($n = 1$).[102] The features described in this section, unless otherwise specified, do not refer to the changes observed at the site of the occlusion and caused by the procedure used to create the RVO itself, but rather those result of the vein occlusion.

All models showed early features classically observed in human BRVO and CRVO, including cessation of blood flow and venous dilation, engorgement, and tortuosity distal to the

Table 6. Parameters of Laser Photocoagulation Used in the Different Animal Models

Animal	Type of Laser	Wavelength, nm	Adjuvant	Power	Duration, s	Size	No. of Shots	References
Mice	Krypton	530.9	IV Rose Bengal (40 mg/kg)	50 mW	3	50 μm	2–3	89
	Yag	532	1 mL 1% fluorescein	200 mW	0.5	50 μm	7–12	90
	N/A	532	IV 0.15 mL Rose Bengal	160 mW	0.8–2.5	50 μm	2–5	91, 92
Rats	Argon	514	IV Rose Bengal (40 mg/kg)	80–150 mW	0.1–0.2	50–100 μm	6–20	68, 69, 73, 81, 83, 96, 217, 220
	Argon	490	IV PAD-S31 (10 mg/kg)	3 mW	N/A	300 μm	N/A	84
	Argon	N/A	IP 0.3 mL 10% sodium fluorescein	100–200 mW	0.2	50 μm	3–5	124
	Argon	N/A	IV 0.2 mL 10% sodium fluorescein	50–100 mW	0.5–1	50 μm	1–12	71, 72, 86, 88
	Diode	532	IV Rose Bengal (20 mg/kg)	100 mW	0.4	75 μm	N/A	70
	Diode	532		180–240 mW	0.4	100 μm	5–7	80
	Diode	675	IV PAD-S31 (10 mg/kg)	3 mW	N/A	300 μm	N/A	84
	N/A	532	IV 2% Erythrosin B (20 mg/kg)	100 mW	0.2	100 μm	5–10	74
Rabbits	Argon	N/A	IV Rose Bengal (40 mg/kg)	90–120 mV150–300 mW	0.2–0.5	50–125 μm	5–20	101, 104, 107
	Argon	532	IV Rose Bengal (40 mg/kg)	150–300 mW	0.5	125 μm	10–30	109, 110
	Argon	N/A	IV Rose Bengal (50 mg/kg)	0.14 mW	0.3	100 μm	5–20	106
	Diode	670	IV CASPc (5 mg/kg)	2 mW		0.5 mm^2		105
Cats	Argon	514		300–500 mV	0.2	200 μm	20–25	116–118
Dogs	Argon	514	IV Rose Bengal (50 mg/kg)	100–150 mW	0.2	100 μm	15–20	126
	Diode	Green	IV Rose Bengal (40 mg/kg)	100–150 mW	0.2	100 μm	15–20	127
Pigs	Argon	514	IV Rose Bengal (10–15 mg/kg)	100–180 mW	1	100–125 μm	4–6	132, 134, 137, 139, 141, 154, 155
	Argon	514		250 mW	0.2–0.5	500 μm	N/A	136, 140
	Argon	532		400 mW	0.5	N/A	20–40	144, 145, 156
	Argon (endo-photocoagulation)	532	IV Rose Bengal (10 mg/kg)	140 mW	0.1	N/A	N/A	146, 147
	Argon	N/A	IV 1 mL 10% sodium fluorescein + PP thrombin	100–20 mW	0.2	200 μm	N/A	142
Nonhuman primates	Argon (coherence radiation 800)	N/A	IV 0.5–2 mL of 10% sodium fluorescein	100–450 mW	0.2	50–100 μm	N/A	192–194
	Argon	N/A	IV Rose Bengal (4 mg/kg)	150–190 mW	5	100 μm	5–7	166
	Argon	Green		400–500 mW	0.5	500 μm	N/A	167, 185
	Argon	N/A		200–500 mW	0.1–0.2	100–200 μm	N/A	186
	Argon	675	IV CASPc	N/A	N/A	300 μm	N/A	159
	Argon	N/A		N/A	N/A	N/A	N/A	129, 157, 158, 176–181
	Xenon arc	N/A		N/A	N/A	N/A	N/A	188, 189
	Dye	577		200–500 mW	0.1–0.3	100–200 μm	N/A	161–165, 184, 186
	Krypton	N/A	IV Rose Bengal (4 mg/kg)	150–190 mW	5	100 μm	N/A	166
	Diode	664	IV NPe6 (2 mg/kg)	N/A	N/A	1200 μm	N/A	82

CASPc, chloraluminium sulfonated phthalocyanine; IP, intraperitoneal; IV, intravenous; N/A, no data available.

occlusion site. Moreover, all models, except the ET-1–induced CRVO, showed retinal hemorrhages and various degrees of retinal edema, which were commonly observed within the first 48 hours of RVO induction,[67,70,74,75,80,83–85,89,90,93,96–99,102,104,108,115,120–122,124–129,132,133,137,139,145,148–152,155–157,167,169,170,178,180,187,189,191,192,195,216,221] peaked at day 4,[70,74,84,98] and resolved 7 to 28 days following occlusion.[70,74,75,89,96,97,102,108,129,156,169,170,172,192,195,221] Various degrees of exudative retinal detachment developed in many eyes of laser-induced and diathermy-induced BRVO [67,74,80,85,89,96,97,105,115,121,124,126,132,186] and laser-induced CRVO eyes.[67,70,174] Bullous retinal detachment also was observed in many models that resolved spontaneously during follow-up.[67,70,74,83,85] Changes in the thickness of the overall retina and individual retinal layers as a result of the edema (thickening) or ischemia (thinning) were evaluated mainly by histopathology[70,74,76,89–92,94,95,114,121,129,131–133,151,154,169,174,179,187,189,190,192]; in five studies, optical coherence tomography (OCT) was used also for this purpose.[75,80,90,91,100] Both CRVO and BRVO models showed significant increase in the thickness of the inner retinal layers 1 to 4 days postinduction, followed by gradual reduction over time, with follow-up periods ranging between 7 and 28 days. In many models, retinal thickness was reduced during the follow-up to values below those detected at baseline (atrophic thinning); this was observed at 7 to 14 days from RVO induction.[75,80,90,91,100]

Branch Retinal Vein Occlusion. *Macular Edema.* Macular edema in the nonhuman primate models was observed as early as 1 to 6 hours following venous occlusion[190,193] and became prominent at 7 to 9 days postocclusion.[180,193] It was found in up to 100% of treated eyes in one of the four studies on nonhuman primate models that described macular edema in induced BRVO (see above).[180] Both intracellular neural and extracellular edema were reported.[190,193] The edema was mainly observed in the nerve fiber layer and outer plexiform layer.[190,193] Capillaries adjacent to the extracellular edema often appeared shrunken or compressed.[190] In addition, macular edema was often associated with photoreceptor cell loss, which persisted after resolution of macular edema.[180,186,193] Spontaneous resolution of macular edema occurred in all occluded eyes between 14 days and 2 year after laser photocoagulation clinically.[180,186,190,193] In one study, histopathologic examination of six eyes at 48 months showed cystic spaces in the outer plexiform layer in four of six eyes.[180]

Retinal Capillary Nonperfusion and Reperfusion. Various degrees of capillary nonperfusion in laser-induced, diathermy-induced, and PD0325901-induced models of BRVO were reported.[70,74,80,85,89,92,97,100,132,133,150,175,179,180,189,191–193,221,222] Areas of capillary nonperfusion were observed as early as 3 days following venous occlusion[85,89] and found to progress with time.[179,192] Extensive or severe areas of capillary nonperfusion were prominent 1 to 4 weeks following vein occlusion[132,187,192,222] and were observed in up to 75% of eyes.[96,133,221] The areas of capillary nonperfusion persisted during the follow-up, which ranged between 1 and 20 weeks, despite reperfusion.[70,80,85,89,92,96,97,132,133,150,175,179,189,191–193,221,222] Reperfusion in these models was either by recanalization/reopening of the occluded vessels in some or all eyes,[70,80,85,89,90,92,93,95–97,104,105,110,112,115,120,126,129,132,133,137,186,187,222] or development of collateral vessels.[85,89,92,96,104,105,120,121,124,129,133,139,175,179,180,183,187,189,192,221,222] Recanalization was observed in 0% to 100% of eyes of BRVO models 1 to 14 days following induction.[70,80,85,89,92,93,95–97,104,105,110,112,126,129,132,137,186,221] Collateral vessels were prominent 5 to 14 days following establishment of the RVO[92,129,179,180,192] (Tables 7, 8).

Neovascular Complications. Posterior segment neovascularization occurred in some laser-induced BRVO models in rodents,[83,89,96] pigs,[132–134,154,221,222] and nonhuman primates,[175,188,189,192] but not in the other BRVO models. Retinal and/or disc neovascularization was observed in 8.3% of eyes as early as 7 days postocclusion,[89] and in 60% to 70% of eyes 14 days following laser induction in rodent models.[83,89] In laser-induced pig models, retinal and/or disc neovascularization were described in approximately 50% to 93% of eyes 3 to 4 weeks following RVO induction[132,133,221,222] and up to 100% of eyes at 6 weeks.[134,154] In laser-induced nonhuman primate models, 9% of eyes developed retinal neovascularization at 4 weeks.[192] Anterior segment neovascularization was observed in laser-induced nonhuman primate models when three major branches were targeted.[176,178,181,184] In this model, up to 100% of eyes developed iris neovascularization within the first 6 days of occlusion[176,178,181,184] and 17% to 20% developed neovascular glaucoma within 25 days of follow-up.[176,178] There was no spontaneous regression during follow-up of 28 to 84 days.[136, 90]

Vascular Endothelial and Pericyte Cell Loss. Damage and loss of the vascular endothelial cells and pericytes was detected by histopathologic examination in experimental animal models of BRVO,[90,107,120,187,190,193] which resulted in ghost acellular vessels with glial invasion[179,187,193] observed as early as 1 to 48 hours postocclusion.[120,190,193] Endothelial cell apoptosis was detected as early as 1 day postocclusion.[90] Pericyte loss was observed 3 days following occlusion and significantly worsened at 7 days with 40% pericyte cell loss detected.[90]

Retinal Atrophy. Atrophy (thinning/loss) of the inner retinal layers[70,74,80,89,91,92,94,95,121,127,132,133,151,154,179,187,189,190,192,193,222] and replacement with glia[151,187] has been reported. The loss of the inner retinal layers was first observed 3 days postocclusion[80] and was marked at 7 to 28 days of follow-up.[70,74,80,89,91,92,95,132,133,151,190,192] Damage of the outer retinal layers and loss of the photoreceptors was observed distal to the site of the occlusion in some eyes with laser-induced BRVO and ischemia at 3 to 6 weeks postocclusion.[132,133,222] Photoreceptor cell loss was observed in 67% of eyes at 3 months following the occlusion[180] Damage to the photoreceptors was reported in photodynamic-induced thrombosis in rats within 2 days of the occlusion, which was most likely related to the photodynamic therapy itself rather than the result of ischemia.[112] Unspecified RPE changes were reported 4 weeks to 3 months following occlusion in laser-induced BRVO nonhuman primate models.[152,180,192]

Functional Changes. When conducted, ERG studies showed reduction of the "a" and "b" wave amplitudes of both scotopic and photopic ERG at 1, 2, 3, 4, 6, and 7 days following laser-induced BRVO in rat models.[80,100] In multifocal ERG, a significant decrease in the P1 and N1 amplitudes and prolonged implicit times in the affected retina were observed 4 weeks following thrombus formation in diathermy-induced BRVO in pig models.[151,152]

Other Features. Other features also were observed in some eyes with experimental animal BRVO, such as cotton wool spots, detected at 3 days to 6 weeks in laser-induced nonhuman primate models,[180,192] venous sheathing between 7 days and 3 months,[125,127,129,152,192] microaneurysms 1 to 8 months,[120,125] and reduction of preretinal oxygen saturation measured at different time points between 60 minutes and 3 weeks following occlusion.[110,121,123,133,150,222]

Central Retinal Vein Occlusion. *Macular Edema.* Macular edema was observed as early as 48 hours following venous thrombosis in 14% to 66% of CRVO nonhuman primate models induced by diathermy.[170,195] This had resolved spontaneously in all eyes 14 days following induction[170,195] (Tables 7, 8).

Capillary Nonperfusion and Reperfusion. Various degrees of capillary nonperfusion were reported in laser-induced,

Table 7. Clinical and Histopathologic Features of BRVO Animal Models

	Success, %	Retinal Hemorrhage	Retinal Edema	MO	CNP	Recanalization	Collaterals	Posterior Segment NV	Anterior Segment NV	Loss of EC/ Pericytes	Loss of IRL	Loss of ORL	RPE Changes	References
Laser photocoagulation														
Rodents	89–100	Y	Y	N	Y	Y	Y	Y	N	Y	Y	N/A	N/A	70, 74, 80, 83–86, 88–92, 96–100, 220
Rabbits	100	Y	Y	N	N/A	Y	Y	N	N	Y	N/A	N/A	N/A	104–107, 109, 110
Cats	100	Y	Y	N	N/A	Y	Y	N	N	N/A	N/A	N/A	N/A	115–118
Dogs	100	Y	Y	N	N/A	Y	N/A	N	N	Y	Y	N/A	N/A	125–127
Pigs	93–100	Y	Y	N	Y	Y	Y	Y	N	N/A	Y	Y	N/A	129–134, 136–142, 144–147, 150–156
Nonhuman primates	100	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	175, 176, 178–181, 184, 187–190, 192, 193
Photodynamic therapy														
Rodents	N/A	Y	Y	N	N/A	Y	N/A	N	N	N/A	Y	Y	N/A	93–95
Rabbits	73	N	Y	N	N/A	Y	N/A	N	N	N/A	N/A	M/A	N/A	112
Cats	50	N	N/A	N	N/A	N/A	N/A	N	N	N/A	N/A	N/A	N/A	119
Pigs	100	Y	Y	N	N/A	N/A	N/A	N	N	N/A	N/A	N/A	N/A	148, 149
Diathermy														
Cats	100	Y	Y	N	Y	Y	Y	N	N	Y	Y	N/A	N/A	120–122, 124
Pigs	100	Y	Y	N	Y	Y	Y	N	N	N/A	Y	Y	N/A	150–153
Intravitreal PD0325901														
Rabbits	N/A	N	Y	N	Y	N/A	N/A	N	N	N/A	Y	Y	N/A	114

CNP, capillary nonperfusion; EC, endothelial cells; IRL, inner retinal layers; MO, macular edema; N, not developed; N/A, not assessed/no data available; NV, neovascularization; ORL, outer retinal layers; Y, developed.

Table 8. Clinical and Histopathologic Features of CRVO Animal Models

	Success, %	Retinal Hemorrhage	Retinal Edema	MO	CNP	Recanalization	Collaterals	Posterior Segment NV	Anterior Segment NV	Loss of EC/ Pericytes	Loss of IRL	Loss of ORL	RPE changes	References
Laser photocoagulation														
Rodents	92–100	Y	Y	N	Y	Y	N/A	Y	N	N/A	Y	Y	Y	68–70, 74, 75, 220
Rabbits	93	Y	Y	N	Y	Y	Y	N	N	N/A	Y	N/A	Y	101
Nonhuman primates	100	Y	Y	N	Y	Y	Y	Y	Y	N/A	N/A	N/A	Y	111, 157–160, 162–167
Diathermy														
Nonhuman primates	N/A	Y	Y	Y	N/A	N/A	N/A	N	N	N/A	Y	N/A	Y	168–173
Permanent mechanical ligation of central retinal vein														
Nonhuman primates	N/A	Y	Y	N	Y	N	N/A	N	N	Y	Y	N/A	N/A	174
Transient ligation/ clamping of optic nerve														
Rodents	N/A	N/A	Y	N	N/A	Y	N/A	N	N	N/A	Y	Y	Y	76, 77, 79
Pigs	N/A	Y	Y	N	N/A	Y	N/A	N	N	N/A	N/A	N/A	N/A	128
Intravitreal thrombin														
Rabbits	43	Y	N/A	N	Y	N/A	Y	Y	N	Y	N/A	N/A	N/A	102
Intravitreal NPe6														
Rabbits	N/A	Y	N/A	N	N/A	N/A	N/A	N	N	N/A	Y	Y	Y	103
Intravitreal ET-1														
Rabbits	100	N	N	N	N	Y	N	N	N	N/A	N/A	N/A	N/A	113

permanent ligation of the central retinal vein, and thrombin-induced CRVO models.[69,108,157,158,162,174] In one of these studies, it was found to become extensive 2 to 4 weeks following the induction of CRVO and progressed to involve up to 75% of the retinal area 7 weeks postinduction of RVO by laser photocoagulation in 67% of eyes.[157] In thrombin-induced CRVO in rabbits, extensive areas of retinal capillary nonperfusion were observed at 3 months following the occlusion.[102] Recanalization or reopening of the occluded vessels was reported in many studies of laser-induced CRVO.[70,74,108,111,157–159] This was observed 1 to 21 days postocclusion[70,74,108,111,159] in 6% to 80% of eyes.[108,111,157,158] Collateral vessels also were reported in some eyes at 2 weeks to 2 months of follow-up following laser-induced and thrombin-induced CRVO.[102,108,157]

Neovascular Complications. Neovascular complications were observed in laser-induced and thrombin-induced CRVO.[68,69,74,102,157–160,162–166] Preretinal neovascularization was observed 1 to 3 weeks following laser photocoagulation in 17% to 90% of rats, with no spontaneous regression described.[67–69,74] In nonhuman primate models, however, posterior segment neovascularization was described in only one study, in which disc neovascularization was detected in 17% of eyes at 15 to 26 days postocclusion that resolved spontaneously at day 87,[157] but not in other studies with follow-up periods ranging between 1 and 24 weeks.[111,158,160,162–167] Thrombin-induced CRVO in rabbits showed retinal neovascularization in 60% of eyes at 3 months following injection.[102] Spontaneous regression of neovascularization in this model was not reported. Iris neovascularization was observed only in laser-induced nonhuman primate models.[157–160,162–166] This was detected 4 to 22 days postocclusion[159,160,162–166] in up to 100% of eyes,[157,163,166] with some having spontaneous regression 13 to 60 days following laser photocoagulation.[157] Iris fluorescein leakage from iris new vessels was observed at 5 days of follow-up in 50% of eyes.[157] Neovascular glaucoma developed in 18% to 33% of eyes in the laser-induced nonhuman primate model 12 to 21 days following occlusion.[158,160]

Vascular Endothelial and Pericyte Cell Loss. Vascular endothelial and pericyte cell loss has not been described in experimental models of CRVO.

Retinal Atrophy. Atrophic thinning of the inner retinal layers and cell loss was reported 7 to 21 days in rodents and rabbit models following laser photocoagulation[70,74,75,101]; 3 to 10 days in diathermy-induced nonhuman primate models, which was in this model associated with gliosis[169]; 3 to 7 days in nonhuman primate models of permanent ligation of the central retinal vein[174]; and 4 days in temporary (60 minutes) ligation of the optic nerve.[76] These changes were not reversible in any of the models during the follow-up, which ranged from 1 to 6 weeks.[70,74–76,169,174] The ganglion cell loss in overall retina (central, midperipheral, and peripheral retinal regions) was reported to be approximately 11% at 7 days,[74] 30% to 31% at 14 days,[70,74] and 40% at 21 days following laser-induced RVO in rodents.[74] Atrophy of the outer nuclear layers distal to the site of laser photocoagulation was reported as early as 4 days following vein occlusion using laser photocoagulation in rodent models.[70,74] RPE changes were observed in many of the CRVO models[76,101,103,157,170] (Tables 7, 8).

Functional Changes. Loss of retinal function in these models was confirmed with ERG studies that showed significant reduction of amplitudes in both scotopic and photopic ERG in laser-induced CRVO in rodents[70] and temporary ligation of optic nerve in rodents.[79]

Other Features. Disc hyperemia was observed within 48 hours in up to 100% of diathermy-induced CRVO in nonhuman primate models, which was secondary to the procedure rather than to the CRVO.[168,195]

Strengths and Limitations of Available Animal Models

Although none of the animal RVO models described above develop all features occurring in human RVO, almost all models demonstrate the early characteristics of this disease, including retinal hemorrhages and edema, which may make them adequate models to study the acute phase of both BRVO and CRVO. Only a few models, however, developed macular edema (i.e., laser photocoagulation in BRVO nonhuman primate models and diathermy in CRVO nonhuman primate models) (Tables 7, 8),[170,180,186,190,193,195] which makes the study of this particular feature difficult.

Most animal models of RVO demonstrated spontaneous reperfusion and/or vascular remodeling, which seemed to occur more rapidly and effectively than in humans with RVO. As a result, persistent ischemic features failed to develop in most models, and iris neovascularization was not observed, except in laser-induced nonhuman primate models,[157–160,162–166,176,178,181,184] making the study of the ischemic form of RVO more challenging. This might be attributed, even if partly, to the fact that the animals used for these studies were young and healthy, whereas patients with BRVO and CRVO are often older and many have underlying systemic risk factors, such as hypertension, dyslipidemia, dysfunctional thrombotic responses, or impaired glucose tolerance/diabetes, among others. The ischemic form of RVO, however, is the one that requires further research more urgently, given its very limited treatment options and often poorer outcomes.

The laser-induced models of BRVO in rodents, pigs, and nonhuman primates and of CRVO in rodents and nonhuman primates were found to be the most successful at achieving nonperfusion and posterior segment neovascularization (see Tables 7, 8). The lack of ischemic features (i.e., extensive areas of retinal nonperfusion and/or neovascularization) being observed in other models may be attributed to the inadequate follow-up time in some of the studies or may be due to other factors such as the nature of the occlusion induced by the various techniques, including duration of the occlusion, and the timing and characteristics of the reperfusion that followed. There are still limitations of the models available that reproduce best retinal ischemia and neovascularization. For example, the laser-induced rodent model of BRVO and CRVO may pose difficulties due to the small size of the eye (Fig.), the large crystalline lens, and the thin and delicate sclera, which may make the undertaking of functional and imaging studies as well as therapeutic interventions challenging. The lack of a macula in many nonprimate models makes it impossible to study macular edema and, although as stated above the occlusion can be produced with high success (92%–100%, see Table 8), neovascularization occurs variably (60%–70% and 17%–90% in models of BRVO and CRVO, respectively). The laser-induced pig model of BRVO appears to be ideal due to anatomic similarities (see Table 4), including the presence of an area centralis, and the high success at achieving vein occlusion (93%–100%) and development of neovascularization (100%) in a relatively short period (6 weeks). Furthermore, the larger size of the eye in this model facilitates functional, structural, and interventional studies. Pigs are larger animals, posing other difficulties (see Tables 3, 5). Nonhuman primate models of laser-induced ischemic CRVO and BRVO best mimic the clinical and histopathologic features observed in humans; however, the use of this species carries major ethical considerations and other inconveniences, such as high cost (see Tables 3, 5) and are not available to most researchers.

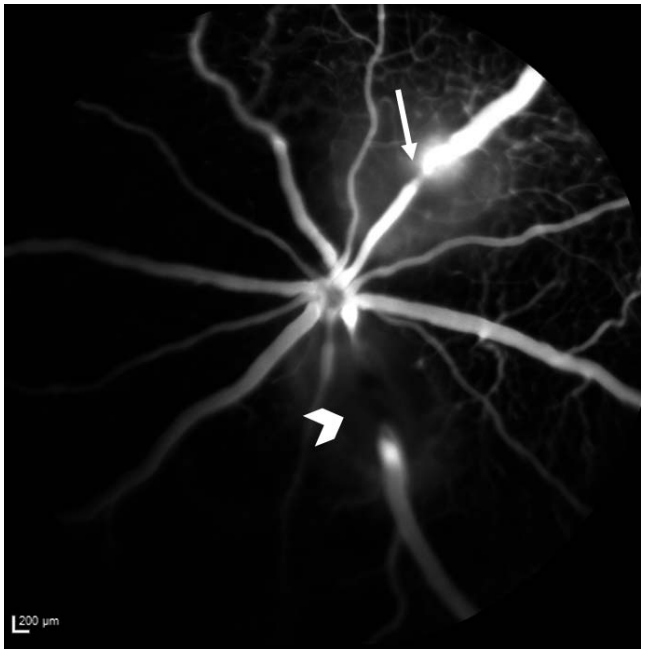

Figure. Fundus fluorescein angiogram obtained in a mouse eye immediately following induction of RVO with laser photocoagulation. Note an area of thinning in a retinal vein at the site of the attempted occlusion, but still presence of flow through the vein (*arrow*). An area of retinal edema blocking the view of the vein itself, which remains perfused, is also seen (*arrowhead*). Achieving a full occlusion of the vein is challenging in mice given that appropriate focusing of the laser beam, even the smallest available, on the very small retinal vein is difficult.

Although thrombin-induced CRVO rabbit models showed ischemic features, namely areas of capillary nonperfusion and development of retinal neovascularization in 60% of eyes,[102] this feature was observed at or after 3 months, which makes the study of the neovascularization in this model time-consuming. In addition, the success rate of developing RVO in this model is as low as 43%,[102] and there are not enough studies in the literature that would allow validating the findings in this model. Similarly, laser-induced iCRVO[101] and PD0325901-induced iBRVO[114] in rabbits do not have adequate supporting literature.

Clinical Value of RVO Models

Although therapeutic strategies are available for people suffering from RVO, these are limited, and a relatively large proportion of patients still lose sight as a result, especially those with iRVO. Treatment is, at present, delivered only once complications (macular edema and neovascularization) have occurred. Thus, it is clear that advances in the management of people with RVO are much needed. Animal models of RVO have helped to better understand the pathogenic events taking place as a result of the disease as well as to trial new treatments. It is likely that several pathways may be implicated in the development and progression of the disease and that different compensatory responses may take place, which would explain the heterogeneity of the natural course and treatment responses observed in humans; experimental animal models of RVO have advanced the knowledge on this area. As retinal ischemia, macular edema, and anterior/posterior segment neovascularization are the major causes of visual loss due to RVO, experimental animal models that more reproducibly develop these complications would be expected to have the major translational potential. Understanding why reperfusion occurs more readily in experimental animal models of RVO when compared with humans with this disorder may provide important clues for the development of new therapeutic interventions.

Conclusions

Several experimental animal models of RVO are available to study the pathogenesis and to test new diagnostic/prognostic/therapeutic interventions for this disease. Selecting the most appropriate ones, based on the information provided in this review, will allow researchers to better adhere to two of the three "Rs" of "reduction" and "refinement," as "replacement" is not an option when understanding the complex events that take place in RVO. It will also help researchers in the development of new treatment modalities by allowing them to select those that mimic more closely the human disease, that develop its features more consistently and in shorter periods of time. This will subsequently reduce testing times and costs and will improve the planning and design of future, more successful studies as well as the potential for translation to clinical practice.

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