Chapter 5

NEOVASCULARIZATION IN MODELS OF BRANCH RETINAL VEIN OCCLUSION

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Abstract: Branch retinal vein occlusion can be achieved in several species using laser photocoagulation with or without photodynamic agents. The neovascular response shows high variability within and between species. However, animal models of ischemia-associated intraocular neovascularization from branch retinal vein occlusion have been employed with success to demonstrate therapeutic effects of pharmaceutical agents and to study mechanisms of angiogenesis.

1. INTRODUCTION

Retinal ischemia is the primary cause of preretinal, optic nerve head, and iris neovascularization (NV) in human ocular disease. Causes of retinal vascular occlusion include diabetes mellitus, radiation, emboli, thrombosis, and inflammation. Occlusions, which can subsequently induce neovascularization, may affect either large or small caliber retinal vessels. Diabetic retinopathy and radiation retinopathy typically produce ischemia by affecting the microcirculation. Large vessel occlusions are identified by the primary site of obstruction: branch or central retinal vein occlusion, and branch or central retinal artery occlusion.

NV, as a complication of retinal ischemia, is highly prevalent in human retinal disease. Diabetic retinopathy (DR) is one of the most common causes of acquired blindness in developed nations, causing about 12% of cases of new blindness in the U.S. annually. Diabetes mellitus afflicts nearly
14 million Americans.\textsuperscript{1} Approximately 5% of all diabetic patients develop ocular neovascularization. Branch retinal vein occlusion (BVO) is the second most common retinal vascular disease;\textsuperscript{2} about 50% of large BVO cases have significant ischemia, and of these about 40% will develop neovascularization.\textsuperscript{3} Central retinal vein occlusions are also common clinical problems; approximately 30% of these cases have severe ischemia, and of these 40 to 60% may also suffer neovascular complications.\textsuperscript{4}

Retinal ischemia can stimulate pathological angiogenesis in multiple ocular tissues, such as the posterior segment (at the optic nerve head or growing out of the retina) or the anterior segment on the anterior surface of the iris. Posterior segment NV requires vitreous to serve as a collagen scaffold for neovascular growth. Importantly, eyes with the vitreous removed by surgical vitrectomy do not develop retinal NV, except where there is persistent vitreous. Posterior segment NV can penetrate the internal limiting membrane to develop along the posterior vitreous face or emanate into the vitreous gel. Posterior segment NV is also associated with a highly variable fibrous component. Typically, the early clinical appearance is that of “naked” vessels growing out of the retina or optic nerve into the vitreous. While these vessels may appear as simple vascular proliferation to the clinician, histopathology invariably demonstrates a fibrous component. With continued proliferation, the fibrous component tends to become more evident as whitish tissue accompanying the vessels. In most cases, untreated preretinal and optic nerve head NV evolves with a time course of months to years. The vessels gradually accumulate fibrous extravascular tissue until the vascular component eventually begins to atrophy and the lesion involutes. During involution, the fibrous component predominates, and the vessels may become grossly unapparent on clinical examination, although histopathology often shows some perfused vasculature.

Blinding complications occur as a consequence of the fibrous component of posterior segment NV. Optic nerve head NV may lead to bleeding into the vitreous cavity. Preretinal NV may also result in vitreous hemorrhage, but in addition, it may lead to a potentially more grave complication: tractional retinal detachment. Vitreous hemorrhage and retinal traction occur when the cellular component of the fibrovascular tissue contracts, causing rupture of the fragile new vessels and detachment of the retina. Vitreous hemorrhage, when mild, may clear spontaneously and cause only mild or transient visual impairment. Severe hemorrhage or tractional retinal detachment involving or threatening the macula can be blinding if left untreated and often requires surgical intervention.

Iris NV, also known as rubeosis iridis, most often develops first as a lacy configuration of vessels around the pupil, on the iris surface, or as small tufts at the pupillary sphincter. In more severe cases, the NV grows across the