A Study of Surgical Approaches to Retinal Vascular Occlusions

William M. Tang, MD; Dennis P. Han, MD

Objective: To develop a surgical approach to retinal vascular occlusive diseases.

Methods: Surgical manipulations were performed on the retinal vasculature to explore the feasibility of retinal vascular surgery. In a human cadaver eye model (25 procedures, 21 eyes), we performed (1) cannulations of retinal blood vessels with a flexible stylet and (2) arteriovenous sheathotomies. Histological findings were correlated with surgical outcomes. In an in vivo model (6 eyes, 5 animals), we examined the technical feasibility and anatomical outcome of surgical penetration of retinal blood vessels.

Results: Cannulations of branch retinal arterioles were successful in 7 of 9 procedures, cannulations of branch retinal venules were successful in 1 of 3 procedures, cannulations of central retinal arteries were successful in 0 of 2 procedures, and cannulations of central retinal veins were successful in 2 of 4 procedures. Arteriovenous sheathotomies were successful in 4 of 7 procedures. In the in vivo model, surgical penetration of retinal blood vessels was accomplished in 5 of 6 eyes. Immediately postoperatively, thrombus formation with obstruction of the retinal vasculature was observed. At 2 weeks postoperatively, the retinal vasculature was completely patent.

Conclusions: Multiple surgical techniques aimed at assisting recanalization of occluded retinal vasculature have been evaluated. Retinal vascular surgery has become more feasible and deserves further investigation.


Retinal artery and vein occlusions are among the most common causes of severe vision loss. In the Blue Mountains Eye Study, the prevalence of retinal vein occlusion was found to be 1.6% in adults aged 49 years or older. Standard treatment is generally ineffective in restoring blood flow.

We are attempting to develop new treatments that might be effective in restoring blood flow in retinal vascular occlusions. We believe that significant therapeutic advances must be directed to the obstructive process in the vascular lumen. The unique opportunity to visualize and access the retinal vasculature during vitreous surgery led us to consider developing an intraocular, endovascular approach to retinal vascular occlusions. Endovascular recanalization procedures such as percutaneous transluminal angioplasty and regional thrombolytic delivery have been effective in restoring blood flow in various organ systems. Timely intervention often results in significant recovery of function. We postulate that intraocular, endovascular therapy can lead to reversal of retinal vascular occlusions.

The technique of endovascular therapy involves 2 important steps: (1) mechanical access of a catheter into the vascular lumen and (2) navigation of the catheter to the desired site of action. We applied this technical concept to the retinal vasculature. In a human cadaver eye model, we developed surgical techniques to (1) gain access into the retinal vasculature and (2) cannulate retinal blood vessels with a flexible stylet. In an in vivo model, we examined surgical techniques for gaining access into the retinal vasculature. The technical feasibility and anatomical outcome of these procedures were evaluated.

Another portion of our study addresses the recent interest in arteriovenous (AV) sheathotomy as a surgical treatment for branch retinal vein occlusion. Investigators have suggested that by mechanical lysis of the AV sheath, compression on the retinal vein might be relieved, leading to reversal of vein occlusion. In the present study, we examined the technical feasibility and anatomical outcome of AV sheathotomy.
MATERIALS AND METHODS

RETINAL VASCULAR CANNULATION: HUMAN CADAVER EYE MODEL

Human cadaver eyes were obtained from the Wisconsin Lions Eye Bank, Milwaukee, and used within 48 hours of expiration. The mean age was 80 years (age range, 63-91 years). The anterior calotte was divided from the posterior calotte at the level of the equator. A total of 18 cannulation procedures (17 eyes) were performed.

Cannulations of branch retinal arterioles, branch retinal venules, central retinal arteries, and central retinal veins were performed. Under microscopic illumination, a bimanual technique with two 20-gauge microvitreoretinal (MVR) blades was used to create an opening in the vessel wall. Approximately 3 to 4 disc diameters away from the optic disc, an MVR blade was introduced to elevate a branch retinal vessel from the surface of the retina. Then, with the first MVR blade acting as a platform beneath the retinal vessel, a second MVR blade was used to make a small longitudinal arteriotomy/phlebotomy incision. In the case of cannulation of the central retinal artery/vein, the same technique was used with the arteriotomy/phlebotomy performed on a first-order retinal arteriole/venule immediately distal to the central bifurcation. A 10-0 black monofilament nylon suture held by a pair of smooth forceps was then used to cannulate the retinal vessel through the arteriotomy/phlebotomy opening. Cannulation was considered successful if the nylon suture could be advanced freely within the lumen of the blood vessel.

After successful cannulation, the specimen was preserved and photographed. Under a dissecting microscope, a block of the posterior eye wall was isolated to include the entire course of the cannulated retinal blood vessel. The specimen was then embedded in paraffin. Tissue sections (5 µm thick) were cut by a keratome in a direction roughly perpendicular to the course of the retinal blood vessels. Every 5th to 50th section was mounted. In the case of the cannulated central retinal vein, tissue sections were cut perpendicular to the axis of the optic nerve. Serial sections were examined to (1) confirm the entry of the nylon suture into the vessel lumen, (2) identify any induced trauma to the endothelial lining due to cannulation, and (3) confirm the extent of vessel cannulation.

RETINAL VASCULAR PENETRATION: ANIMAL EYE MODELS

All animal research protocols were reviewed and approved by the Animal Research Committee of the Medical College of Wisconsin, Milwaukee. In total, 6 eyes were operated on: 4 eyes from 3 rabbits and 2 eyes from 2 dogs. The rabbit was selected because of the presence of a retinal vascular system. The dog was selected because the caliber of its retinal blood vessels more closely approximates that in humans.

Three-month-old New Zealand white rabbits (2.4-3 kg) were obtained through the Animal Research Facility at the Medical College of Wisconsin. Ketamine (44 mg/kg) and xylazine (5 mg/kg) were injected intramuscularly to provide sedation and akinesia, respectively. Standard sterile surgical techniques were employed. Illumination was provided by the coaxial light source from an operating microscope. A 2.5-mm infusion cannula was placed through the pars plicata at the inferotemporal quadrant. The retina was visualized through an irrigating contact lens. An MVR blade or a sharpened metal wire held by a pair of intraocular forceps was introduced through the pars plicata. A retinal vessel along the temporal myelin wing, at approximately a third of a disc diameter from the optic disc, was penetrated. (Because of the similarity in color and size of the retinal arterioles and venules, the retinal vessel selected for penetration was not specified as an arteriole or a venule.) Visualization of a small burst of blood extravasating into the vitreous cavity indicated successful penetration. Intraoperative bleeding was controlled by raising the intraocular pressure for 60 seconds via elevation of the infusion bottle. Rabbit 1 underwent a bilateral procedure and was killed immediately by intravenous injection of pentobarbital/phenytoin solution (1 mL per 5 kg). Two other rabbits underwent survival procedures. Fundus examinations by indirect ophthalmoscopy were performed at weeks 1 and 2 after surgery. Fundus photographs were taken at week 2. The rabbits were then killed with pentobarbital/phenytoin injection. The globes were promptly enucleated.

Adult hound dog eyes were operated on during a nonsurvival experiment simultaneously conducted by cardiovascular physiologists studying coronary blood flow. Anesthesia was maintained by intermittent doses of intravenous pentobarbital (200 mg/kg) and barbital (26 mg/kg). Systemic medications relevant to our surgical procedure included intravenous heparin. Surgical penetration of a retinal venule was performed as described earlier. Both eyes were enucleated immediately after surgery.

After preservation, the posterior calotte was isolated. A surgical blade was used to cut perpendicularly to the direction of the retinal blood vessels to remove tissue ½ to 1 disc diameter peripheral to the vessel penetration site. The specimen was then embedded in paraffin, with the cut edge marked for keratome sectioning (section thickness, 5 µm). For a distance of 1000 to 1500 µm spanning the vessel penetration site, every fifth section was mounted. Otherwise, every 10th to 100th section was mounted. Serial sections were examined to determine the integrity of the retinal vasculature, as well as the presence of associated retinal abnormalities.

AV SHEATHOTOMY: HUMAN CADAVER EYE MODEL

Human cadaver eyes were used as described earlier. Seven AV sheathotomy procedures (6 eyes) were performed. Arteriovenous crossings were selected from a first- or second-order arteriole at a location where the blood vessel was sufficiently filled with blood to allow for visualization during dissection. Under microscopic illumination, an MVR
blade was introduced to gently elevate the arteriole on each side of the AV crossing from the surface of the retina. Then, with a sawing motion of the MVR blade, the AV sheath was engaged. In one case, a pair of intraocular scissors was used to divide the AV sheath. The AV sheathotomy was considered successful if the MVR blade or intraocular scissors could be passed freely between the arteriole and the venule. The branching patterns of the retinal blood vessels were recorded in the form of a carefully drawn sketch to facilitate identification of the sites of the AV sheathotomies during histological preparation.

After successful AV sheathotomy, the specimen was preserved and photographed. Under a dissecting microscope, the site of the AV sheathotomy was identified. A block of posterior eye wall (approximately 4 × 4 mm) was isolated, with the site of the AV sheathotomy located in the central portion of the tissue block. Histological sections were prepared as described earlier. For a distance of 1000 to 1500 µm spanning the site of dissection, every 5th section was mounted; otherwise, every 10th to 100th section was mounted. Serial sections were examined to (1) confirm complete lysis of AV adhesion, (2) identify any induced trauma to retinal vessels, and (3) identify any induced trauma to the adjacent retinal tissue.

**RESULTS**

**RETINAL VASCULAR CANNULATION: HUMAN CADAVER EYE MODEL**

Cannulations of branch retinal arterioles, branch retinal venules, and central retinal veins were successfully performed (Table). In cases of successful cannulation of branch retinal vessels, the nylon suture could be advanced with ease toward the center of the optic disc (Figure 1). However, the suture would not bend sufficiently to allow further advancement into the optic nerve. In cases of successful cannulation of the central retinal vein, the suture could be advanced with ease into the optic nerve (Figure 2). The suture was then observed to emerge from the stump of the retrobulbar optic nerve. Factors responsible for unsuccessful cannulation included: (1) insufficient blood fill in the retinal vessels, precluding adequate visualization; (2) obscuration of view due to extravasated blood during dissection; (3) inability of the nylon suture to gain entry through the arteriotomy/phlebotomy sites; (4) false passage into subretinal space after multiple attempts; and (5) folding and distortion of the retina. Histological examination of successfully cannulated specimens demonstrated a nylon suture fragment inside the retinal blood vessel with no observable damage to the endothelial lining (Figure 3). In the case of cannulation of the central retinal vein, the nylon suture fragment could be identified in the central retinal vein at the level of the lamina cribrosa (Figure 4).

<table>
<thead>
<tr>
<th>Procedure*</th>
<th>No. of Successful Procedures/Total Procedures</th>
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<tr>
<td>Branch retinal arteriole cannulation</td>
<td>7/9</td>
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<tr>
<td>Branch retinal venule cannulation</td>
<td>1/3</td>
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<tr>
<td>Central retinal artery cannulation</td>
<td>0/2</td>
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<tr>
<td>Central retinal vein cannulation</td>
<td>2/4</td>
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<tr>
<td>Retinal vascular penetration</td>
<td>5/6</td>
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<td>Arteriovenous sheathotomy</td>
<td>4/7</td>
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* Retinal vascular penetration was performed on an animal eye model; all other procedures were performed on human cadaver eye models.
Immediate Anatomical Outcome

Four eyes were enucleated promptly after surgery. Histological evaluation demonstrated thrombus formation in a retinal arteriole (left eye of rabbit 1, Figure 5), or a retinal venule (right eyes of rabbit 1 and dog 1). In 2 cases (right and left eyes of rabbit 1), the vascular penetration site could be identified (Figure 5). In dog 2, except for the presence of vitreous hemorrhage, histological findings were normal.

Survival Surgery

In the 2 eyes from animals undergoing survival surgery, fundus examination at week 1 and 2 demonstrated a normal-appearing retina with a clear vitreous cavity in one (rabbit 2), and a normal-appearing retina with an inferior vitreous hemorrhage in the other (rabbit 3). Histological examination of the eye from rabbit 2 demonstrated a completely patent retinal vasculature (Figure 6). Evidence of previous surgical trauma included a few erythrocytes in the vitreous cavity and a few subretinal macrophages adjacent to a small outer-layer retinal dehiscence. Histological findings in rabbit 3 were similar to those in rabbit 2.

AV SHEATHOTOMY: HUMAN CADAVER EYE MODEL

Arteriovenous sheathotomy was successful in 4 of 7 procedures (6 eyes). During the dissection, it was observed that the adhesion between the arteriole and the venule was surprisingly strong, so much so that the adjacent retina was often dragged when the AV sheath was being engaged. In unsuccessful cases, the retina was either dragged to an unacceptable degree or a retinal blood vessel was transected. Histological examination of successfully operated specimens demonstrated a complete lysis of the AV adhesion (Figure 7). However, in the case performed with intraocular scissors, a laceration was observed on the retinal venule wall. In 2 cases, a full-thickness retinal break near the site of dissection was observed.

COMMENT

Endovascular recanalization therapy has demonstrated efficacy for vascular occlusions in various organ systems, including the heart, brain, and extremities. Endovascular therapy can help reestablish blood flow by mechanical or pharmacological means. Percutaneous transluminal angioplasty is the classic mechanical approach in which the thrombus or the atherosclerotic...
plaque is physically disrupted by an angioplasty balloon. {19} Alternatively, regional infusion of a thrombolytic agent can result in pharmacological lysis of the thrombus. {8,9} The unique opportunity to visualize and access the retinal vasculature during vitreous surgery led us to consider an intracocular, endovascular approach to retinal vascular occlusions. The present study on cannulation of retinal blood vessels demonstrates the technical feasibility of (1) mechanical access into the retinal vasculature and (2) the introduction and advancement of a flexible stylet to a potentially desired site of action.

During the preliminary phase of the study, we experimented with a variety of materials for penetrating retinal blood vessel walls, including nylon sutures, thin metal wires, glass micropipettes, and MVR blades. We noted that the penetrating tip of the material must be extremely sharp to allow for reliable penetration without significant distortion to the adjacent retina.

Selection of stylet material is another issue integral to successful cannulation. In the preliminary phase, we experimented with 10-0 nylon, 11-0 nylon, 11-0 polyester (Mersilene; Ethicon Inc, Somerville, NJ) and 10-0 polypropylene sutures (Prolene; Ethicon Inc), and found that 10-0 nylon sutures provided the most reliable cannulation. The 11-0 polyester sutures had a tendency to bend and kink inside the blood vessel; the 10-0 polypropylene sutures were too floppy for reliable entry into the blood vessel. The degree to which a flexible stylet can reach various locations in a branch retinal vessel is important because pathological entities such as venous thrombi and thromboemboli are often localized to specific sites within the vasculature. {3,13} Starting from a distal branch retinal vessel, we were unable to navigate the 10-0 nylon suture beyond the center of the optic disc, because the nylon suture was not flexible enough to make an acute turn from the plane of the fundus into the axis of the optic nerve. However, we were able to cannulate the central retinal vein by accessing a first-order venule on the optic disc. Successful cannulation of the central retinal vein is significant because the obstructing thrombus in central retinal vein occlusion has been localized to the level of the lamina cribrosa. {6} A desirable stylet material in the future should therefore be flexible enough to conform to the curves and turns of the retinal vasculature, but rigid enough to allow for navigation without kinking and mechanical disruption of the thrombus.

In addition, successful cannulation with a flexible stylet leads to the consideration of future cannulations performed with a microcatheter, through which thrombolytic agents can be infused. Regional thrombolytic infusion as potential therapy for retinal vascular occlusion deserves important consideration, because its efficacy has been demonstrated in other organ systems. {8} Delivery of thrombolytics into the ophthalmic artery via a transfemoral route has been reported to be effective in some cases of central retinal artery occlusion. {14,15} Recently, with the assistance of a microcannulator, intravitreal injection of thrombolytics into a branch retinal venule has been reported for central retinal vein occlusion. {16}

Our animal study examined the issue of gaining surgical access into the retinal vasculature under in vivo conditions. Using a manual technique, a small, controlled penetration of a retinal vessel can be accomplished without necessarily causing persistent thrombosis at the penetration site. Such a maneuver is essential to obtain mechanical access into the retinal vasculature. The possibility of an uncontrolled intraoperative hemorrhage from the injured retinal vessel was a concern. In each case, hemostasis was maintained after raising the intraocular pressure for 1 minute. The present study is limited to penetration of the retinal vasculature using a single-handed technique. In the future, a bimanual technique could be employed: a sharp instrument in one hand could penetrate a retinal vessel, and a blunt stylet or microcatheter in the other could cannulate the vessel. Maintenance of hemostasis would certainly be critical and could be accomplished by adjustment of intraocular pressure and other techniques such as intravitreal injection of a perfluorocarbon liquid. {17}

Our study of AV sheathotomy addresses the peculiar anatomy of AV crossings and a potentially viable surgical technique for branch retinal vein occlusion. At the site of an AV crossing, the arteriole and the venule share a common adventitial sheath, with the venule often apparently compressed, or its course acutely diverted, by the arteriole. {18,19} It has therefore been speculated that thrombus formation in the retinal venule is caused by chronic compression from the adjacent arteriole. {20} A case series suggested that AV sheathotomy might lead to decompression of the retinal venule and reversal of branch retinal vein occlusion. {21} Histological data were not available to demonstrate the ana-
A look at the past . . .

The putting into practice by a beginner of the teaching received from a first-class master, may prove interesting and instructive to some of the readers of these ARCHIVES, hence my presentation to them of this report of my first one hundred cataract extractions. These have been performed at several of the general and private hospitals of this city, and at the private residence of a good many of the patients, the nursing often leaving a good deal to be desired, making the fair amount of success with which they have been attended all the more satisfactory. This I attribute, in great part, to the putting into practice by a beginner of the teaching received from a first-class master, may prove interesting and accomplishing such surgical goals. Once the retina vasculature is accessed, a variety of therapeutic approaches, both mechanical and pharmacological, can be pursued.


REFERENCES