Induced chorioretinal venous anastomosis in experimental retinal branch vein occlusion

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Abstract

Iatrogenic retinal vein to choroidal vein anastomoses were created using laser photo-coagulation in six of seven dog eyes in which a partial branch retinal vein occlusion had previously been created photochemically. A similar attempt to create an anastomosis was made in six control eyes in which no branch vein occlusion was present. In the eyes in which a branch retinal vein had been created, a venous chorioretinal anastomosis appeared to be present by 3 to 6 weeks. In three control eyes similar venous anastomosis was created; however this took 6 to 8 weeks to develop and was of much smaller calibre than the one that developed in the presence of a partial branch retinal vein occlusion. No adverse complications were noted in the period of the study (3 months). This study demonstrates that chorioretinal venous anastomoses can be created and may be of use in the treatment of partial retinal vein occlusions that show signs of progression.

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Retinal venous occlusive disease is a common cause of visual loss in the elderly and in those with hypertensive and/or arteriosclerotic vascular disease. The occlusion is thought to be caused by an intraluminal venous thrombosis which produces a variable degree of obstruction to venous outflow. Depending upon the degree of obstruction, the clinical features of a partial or complete occlusion are produced. In the complete form there is irreversible retinal ischaemia and severe visual loss occurs. In the partial form, a variable degree of venous stasis occurs and the capillary vasculature remains largely intact. In this latter group, visual loss is often initially less severe, and is usually caused by retinal oedema secondary to the incompetence of the capillary circulation owing to the raised intraluminal venous pressure.

Retinal venous occlusions may occur in either the central, a hemiretinal, or a branch retinal vein. In each case in the initial stages, the only channel for the venous blood to exit the eye is blocked to a varying degree. In the later stages of the disease, some collateral circulation may develop, but often by this time the potential for full visual recovery has been lost due to irreversible changes in the macular region. These usually take the form of varying degrees of ischaemia, cystoid macular oedema, pigmentary dispersion, or preretinal fibrosis. In the cases of branch or hemiretinal retinal vein occlusion, these collaterals may take the form of a vein to vein anastomosis to bypass the occluded segment with the venous blood then exiting the eye through the central retinal vein. In a central retinal vein occlusion, however, the only possibility of bypassing the obstruction would be the development of a venous anastomosis between the retinal and choroidal circulations. Such connections may occur at the disc as opticociliary anastomosis, however these are slow to develop and do not form in all cases. This study explores the possibility of creating an iatrogenic anastomosis between the retinal and choroidal venous circulations distal to the disc in an experimental model of a branch retinal vein occlusion. If collateral vessels such as these can be induced to occur between a high pressure circulation such as exists with an obstructed retinal vein and a low pressure circulation such as the choroidal venous system, the prevention of a closed loop circulation and its ischaemic consequences may result.

Materials and methods

Branch retinal vein occlusions were created in one eye in nine mongrel dogs (7.0–20 kg) aged from 8 to 18 months. All experimental procedures were carried out under intravenous thiopentone and nembutal anaesthesia by controlled continuous intravenous infusion. Further ocular anaesthesia was obtained by topical 1% amethocaine eye drops and local subconjunctival injection of 1% lignocaine to ensure that the area to be grasped by fixing forces was adequately desensitised. Pupils were dilated with phenylephrine hydrochloride (10%) and tropicamide (1%) eye drops for all procedures.

The branch retinal vein occlusion was created in the inferior retina of one eye in each dog away from the tapetal area. A focal thrombosis was induced photochemically in an inferior branch retinal vein using argon green laser light at 514 nm and intravenous rose bengal (50 mg/kg). A small segment of the retinal vein, one disc diameter away from the disc, was irradiated with the argon laser via a contact lens using a power setting of 100–150 mW with a duration of 0.2 seconds and a spot size of 100 µm. This was performed while the rose bengal was either in full venous circulation or in a recirculation phase. Approximately 15 to 20 applications were required to stop the blood flow in the thrombosed vessel. Following this, engorgement of the distal vein was noted with the development of scattered intraretinal haemorrhages within its drainage area. Immediately after the occlusion was created, a high intensity small spot size laser burn (50 µm at 1.0 to 1.5 W and with a duration of 0.1 seconds) was placed over a small peripheral tributary vein in the drainage distribution of the occluded vein. The aim was to disrupt the
vessel, the underlying retinal pigment epithelium, and Bruch’s membrane, and to produce a small chorioidal haemorrhage. In the other eye a similar small laser burn was placed over a small tributary vein in the distribution of an inferior branch retinal vein.

Early lyis of the thrombosis was prevented by the administration of tranexamic acid 25 mg/kg orally four times a day for 3 weeks. Fluorescein angiograms and fundus photographs using a fundus camera (60° Canon CF602A) were performed before the photothrombosis and at 1, 2, 4, 6, 8, and 12 weeks.

The animals were sacrificed by Lethobarb injection at the conclusion of the study. The eyes were immediately enucleated, bisected, and their posterior segments fixed in 2.5% glutaraldehyde in phosphate buffer and prepared for light and electron microscopic studies. Specimens of full thickness retina and choroid were then taken from the site of the high intensity laser burn where the developing chorioretinal anastomosis was present. The specimens were thereafter post fixed in osmium tetroxide, dehydrated, and embedded in epoxy resin. Serial sections, 2 μm thick, were taken and stained with toluidine blue for light microscopic studies. Ultrathin sections stained with uranyl acetate and lead citrate were used for electron microscopic studies.

A further animal was sacrificed 1 hour after a branch retinal vein occlusion was created photochemically. Specimens of full thickness retina and choroid were then taken from the region of the irradiated vein for histological study to confirm that an occlusion had been created.

Results
Partial retinal branch vein occlusions were created in seven of the nine eyes. In the remaining two eyes complete branch retinal vein occlusions were created which caused a localised serous retinal detachment. This serous detachment lasted only 1 to 2 weeks. However the retinochoroidal separation prevented a chorioretinal anastomosis developing at the site of the high intensity laser burn. In the seven eyes in which a partial branch retinal vein occlusion was created, a venous chorioretinal anastomosis occurred at the site of the high intensity laser burn in six eyes. By 3 to 6 weeks, fluorescein angiograms appeared to demonstrate blood flow from the retinal vein into the choroidal circulation at the site of the high intensity laser burn in all six eyes (Fig 1). The size of the venous chorioretinal anastomotic vessel increased progressively over the following weeks. Both the proximal and distal parts of the vein were seen to drain into the choroid. Retrograde flow was seen in the proximal vein with blood flowing away from the disc to the site of the anastomosis (Fig 2). Following the photothrombosis, the area of the retinal vein irradiated remained narrow but patent in the seven eyes with partial branch retinal vein occlusions. In the six eyes in which a chorioretinal anastomosis was successfully created, the proximal part of the vein progressively narrowed to the point of total occlusion over 2 to 3 months as the chorioretinal anastomosis developed. The area of total occlusion was usually just distal to the area irradiated with the laser.

In the fellow eyes, high intensity control laser burns were placed in six eyes over a similar small venous tributary in the drainage distribution of an inferior branch retinal vein. In three (50%), a chorioretinal venous shunt was created. Definite fluorescein angiographic evidence demonstrating flow into the choroid was seen at 6 to 8 weeks in all three eyes. The size of the anastomotic vessel was smaller compared with the eyes in which a branch retinal vein was first created. Some narrowing of the proximal portion of the vein was seen as the anastomotic vessel developed; however this did not progress to the stage of complete closure.

Histological examination of the eye enucleated...
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by fluorescein angiography an anastomotic vessel was detected by serial sections taken at 2 μm intervals. This vessel connected a retinal vein to a choroidal vein and was usually of large calibre (100 μm) (Fig 5). Surrounding the chorioretinal anastomotic vessel was a dense full thickness chorioretinal scar composed of proliferated retinal pigment cells, gliotic tissue and pigment laden macrophages. Significant persistent subretinal or retinoiretinal neovascularisation in the area surrounding this scar was not seen in this study.

Discussion
The current therapeutic options for the treatment of retinal venous occlusions are limited in their effectiveness and are mainly non-specific in that they fail to address the basic pathological process causing the obstruction in the retinal vein. In the case of a branch vein occlusion the obstruction lies in the vein, usually at a point where it is crossed over by an artery.7 In a hemiretinal vein occlusion the obstruction lies in one of the dual retinal venous trunks as it exits the optic disc. Finally, in the case of a central retinal vein occlusion the obstruction lies in the central retinal vein in the region of the laminar cribrosa.8 In each case the obstruction is owing to an intraluminal thrombus plus secondary factors such as endothelial cell proliferation. This obstruction blocks venous outflow to a variable degree, producing either a complete or partial obstruction. Where a complete obstruction has occurred there exists in the affected area of the retina a closed loop circulation with consequent ischaemia, capillary loss, and cell death. In this form there is little or no prospect for improvement of function in the affected area once eventual recanalisation occurs. Treatment for complete occlusions consists of laser photoagulation of the ischaemic area with the aim of preventing neovascular complications rather than the restoration of vision.9 In the partial retinal vein occlusions venous outflow is not completely blocked and in the initial stages there is usually little or no ischaemia and capillary loss. This does change with time as the intraluminal thrombus causing the obstruction may propagate, increasing the level of obstruction, or undergo recanalisation. In partial venous occlusions therefore there is often a period of time available where it would be possible to intervene and reduce the level of obstruction should such a therapeutic option exist.

In the case of the central retinal vein occlusions the partial form is the more common (54–78%).10 In this group 40% will have resolution of the occlusion and a return of near normal vision. A further 40% will eventually develop normalisation of retinal circulation but will be left with chronic macular oedema and impairment of vision. The remaining 20% will progress to the complete form.11 In those that do progress from the incomplete to the complete form, the time of transition may vary from 1–5–26 months with a median of 4–5 months.12 Serial parameters such as funduscopy, fluorescein transit times, estimation of central retinal venous pressure by ophthalmodynamometry, and electroretinography

1 hour after photothermosis of a retinal vein confirmed that a total occlusion was present at that time (Fig 3). Clinically in the other eyes in the series that were allowed to progress, the vein appeared to have partially reopened by 1 to 2 days and this was confirmed by the fluorescein angiogram that was performed at 1 week. Despite the use of rose bengal as a photothrombotic agent and lower laser energy powers, histological examination showed destruction and necrosis in the surrounding retina and severe damage to the vessel wall as well as an intraluminal thrombus (Figs 3 and 4).

At the conclusion of the study (3–4 months) the eyes were enucleated and the area of the high intensity laser beam was examined histologically. In the six eyes in which blood flow from a retinal vein into the choroid was demonstrable.
with finely granular platelet material (*). These have been used in the past. These have no scientific basis and not surprisingly were ineffective. Ocular hypotensive agents may improve retinal blood flow by lowering venous resistance but offer no sustained benefit. Anticoagulants have also not proved effective. As thrombus organisation and endothelial cell proliferation may occur quite early their potential benefits would seem to be limited. Corticosteroids may help to reduce macular oedema in the short term by reducing endothelial cell permeability but as there is no direct evidence that a vasculitis of the central retinal vein is the primary cause of the occlusion it would appear that they also offer no long term benefits. Indeed, Green et al have demonstrated that the chronic inflammatory infiltrate found in the region of the thrombus in the central retinal vein is a result of the occlusion rather than the cause.

Thrombolytic agents such as streptokinase have been associated with an unacceptable incidence of severe side effects and are no longer used. New agents such as tissue plasminogen activators, which are clot selective and do not have an effect on circulating plasminogen, offer a theoretical advantage but the results of clinical trials remain to be seen. Isovolaemic haemodilution has been shown to improve visual acuity in a study on non-ischaemic central retinal venous occlusion. The improvement is probably due to reduced blood viscosity allowing improved retinal microcirculation. There is no effect, however, on the degree of obstruction to venous outflow.

None of these forms of treatment are currently widely used either due to a lack of effectivity or deleterious side effects. Central retinal venous occlusion is thought in most cases to be caused by compression of the vein in the region of the lamina cribrosa by a thickened and more rigid arterial wall as a result of systemic hypertension and/or arteriosclerosis. This leads to turbulence causing endothelial damage in the retrolaminar portion of the vein and subsequent platelet aggregation and thrombosis. Endothelial cell proliferation and organisation of the thrombus then occurs and later recanalisation may develop, but by this time irreversible visual loss may have occurred. There is outflow obstruction in central retinal venous occlusion and the only therapeutic modalities mentioned above which have shown some degree of success either try to lyse the thrombus or, by reducing viscosity, enable the blood to exit through a partially occluded lumen. Even though theoretically these might help in the short term, the initial predisposing factors remain in the region of the lamina cribrosa. The patient is therefore placed at continued risk of either a new thrombus developing which may progress to a complete occlusion and/or the risks of systemic complications of the treatment — for example, fibrinolics.

Recurrent thrombosis has been confirmed histologically in a large series where in some eyes the formation of a fresh thrombus immediately posterior to an older recanalised fibrotic thrombus was noted.

In order to be effective, the form of treatment...
to be used must permanently improve the retinal circulation and the currently available ones fail to do this. Alternative pathways for venous blood to exit the eye may have to be considered rather than concentrating on ways to force it through what is probably a permanently damaged central retinal vein. Such pathways may occur at the disc as opticociliary anastomoses in vein occlusions; however these do not occur in all patients and may take considerable time to develop. Other such connections between the retinal and choroidal circulation may occur away from the disc and have been reported in association with inflammatory chorioretinal scars,\textsuperscript{21-26} age-related macular degeneration associated with subretinal neovascularisation,\textsuperscript{25,27} penetrating trauma,\textsuperscript{28} choroidal rupture,\textsuperscript{29} and meridional folds at the ora serrata.\textsuperscript{30} Chorioretinal anastomoses have also been induced experimentally with laser photocoagulation.\textsuperscript{31} This study by Wolf and Goldberg explored the possibility of reperfusing experimentally occluded retinal arterioles using intense photocoagulation to create a chorioretinal arterial anastomosis. They were successful in nine out of 19 sites with the time required for the establishment of the anastomosis ranging from 7 weeks to 9 months. In our study an attempt was specifically made to create a retinal vein to choroidal vein anastomosis. This was done by first creating a partial venous occlusion thus raising the intraluminal pressure to encourage the passage of blood into the lower pressure choroidal venous circulation. The site of the anastomosis was placed in the mid-periphery away from the posterior ciliary arteries and larger choroidal arteries to lessen the likelihood of a choroidal artery to retinal vein connection. In the seven eyes in which a partial branch retinal vein occlusion was created a venous chorioretinal anastomosis was successfully induced in six eyes. Evidence of blood flow from the retinal venous circulation into the choroid was demonstrable by 3 to 6 weeks in all eyes by fluorescein angiography. As discussed earlier, most partial central retinal vein occlusions that progress to the complete form do so over a period of 1.5 to 4.5 months.\textsuperscript{32} In this series a retinochoroidal venous anastomosis was induced and appeared to be functioning 3 to 6 weeks after a partial branch retinal vein occlusion was created. This is before most partial central retinal vein occlusions observed clinically progress to the complete form and this technique may therefore be useful in the management of such occlusions which show signs of increasing outflow obstruction. Even though in this series the anastomosis was created in a partial branch retinal vein occlusion, the establishment of a retinochoroidal venous anastomosis, distal to the site of the thrombosis in other forms of retinal vein occlusions, should relieve the outflow obstruction and allow the retinal venous pressure to return to normal. The site of the obstruction in a central retinal vein occlusion lies at the level of the lamina cribrosa proximal to the anastomosis of the superior and inferior venous circulation on the optic disc. This would allow the passage of venous blood from one hemisphere into the other and out through the chorioretinal anastomosis.

In this series the creation of a partial branch retinal vein occlusion before the attempt to create a chorioretinal venous anastomosis appeared to increase the likelihood of a successful anastomosis occurring. Venous chorioretinal anastomoses were created in six out of seven eyes in which a partial branch retinal vein occlusion was created first, and in only three out of six control eyes. In addition, the anastomosis developed at an earlier stage in the experimental eyes and appeared to carry a higher volume of blood. This is illustrated by the fact that in the eyes with the partial branch retinal vein occlusion the proximal part of the vein narrowed to the point of total occlusion over 2 to 3 months. This narrowed segment included the segment treated with laser to create the initial photothermolysis and a portion of the vein distal to it, and was presumably caused by a progressive vascular steal as a chorioretinal anastomosis developed and the pressure differential between the retinal and choroidal veins lessened. In the control eyes, over the same period, some narrowing of the proximal vein was seen but this did not progress to the stage of complete closure. The prior establishment of a partial branch retinal vein occlusion thus raising the intraluminal venous pressure in one group appears to increase both the likelihood and the speed of development of a venous chorioretinal anastomosis in response to a high intensity laser burn over one of the tributary veins.

In this animal model a reproducible venous chorioretinal anastomosis could be created and no significant complications from the high intensity laser burn were seen. To create the shunt the laser energy has to be sufficiently intense to disrupt Bruch's membrane, allowing vessels from the choroid to anastomose with the disrupted venous tributary. The higher pressure in the obstructed vein should then encourage the formation of a larger anastomotic vessel into the choroid. Although not seen in this small

Figure 5 Light photomicrographs showing a large choroidal vein (CH) with an anastomosis to a retinal vein (RV). The anastomotic vessel is surrounded by glotic tissue (G), proliferated retinal pigment epithelial cells (P), and pigment laden macrophages (M). The venous shunt is of large calibre (approximately 100 μm) and connects to a similarly large choroidal vein (toluidine blue, magnification ×270).
series, the potentially serious complications of choroidal neovascularisation arising through the laser-created defect in Bruch's membrane could occur. Serous or haemorrhagic detachments of the retinal pigment epithelium, sensory retina, or both could occur as well as progressive exudation, inflammation, and organisation leading to a subretinal cicatrix. Subretinal neovascularisation leading to large vascular complexes and scarring involving the retina and even extending into the vitreous have been reported after experimental disruption of Bruch's membrane with laser photocoagulation.\textsuperscript{32,33} Significan subretinal neovascularisation around the site of the high intensity laser burn was not seen in our series. Perhaps the rapid establishment of a larger channel may have caused regression of the remaining neovascular fronts growing through the defect in Bruch's membrane by shunting blood away from them.

In conclusion, the establishment of a retinochoroidal venous anastomosis distal to the site of the thrombosis in retinal venous occlusions should relieve the outflow obstruction and allow the retinal venous pressure to return to normal. If this can be created in a partial retinal vein occlusion prior to its transition to the complete form, the potential for some return of visual function remains. Further long term studies are being conducted to evaluate fully the effect of the retinal vein to choroidal vein anastomosis on the evolution of retinal vein occlusions and to the possible development of complica-

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