An interesting finding can be related to the angiogenesis process. Ozdemir and colleagues[9] found that nitric oxide levels (NO) are lower in pterygium tissue than in normal conjunctiva. This fact might be the result of hyperirrigation of blood by the rich vascular net of the pterygium. This is opposite to the ischaemic conditions through which NO levels rise.

Naib-Majani and colleagues, in an immunohistochemical study,[10] presented results on the distribution of the extracellular matrix in pterygium. It was found that collagens III and IV were expressed, while collagens I, II, and VII were missing. Heparan sulfate was strongly expressed in blood vessel walls and epithelial membranes. The study indicates an active involvement of MMPs 8, 9, and 13 in the pathogenesis of pterygium.

An overall view of the growth process of pterygium reveals a multiplicity of factors that are correlated and interrelated. Di Girolamo and colleagues[11] show, in an overview of the pathogenesis of pterygium, that the cytokines, growth factors, and MMPs are the main groups involved in that process. Climatic and geographical location are factors inducing the appearance of pterygium.[12 13]

We can observe three main factors that lead to the final product, the pterygium—mitogenity, construction of a new vascular net, and remodelling of the extracellular matrix. Altogether they create a new vascular and fibrotic tissue, which has an aggressive way of growing to and over the cornea. Today, surgical removal is the common way to treat pterygium, but the recurrence rate is reported to be high.[14]

It might be that understanding the biochemical process, which takes place in the growth of pterygium, can lead to the development of topical medications that may prevent or stop the pterygium in its early stage.

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Cyclophotocoagulation

Endoscopic and transscleral cyclophotocoagulation

P A Bloom, S Dharmaraj

Current status

Diode laser transscleral cyclophotocoagulation (TSCP, or cyclodiode as it is commonly known in the United Kingdom), has become a popular minimally invasive treatment for glaucoma. Initially this modality was used only in eyes with advanced end stage glaucoma and with little or no visual potential, where most other surgical treatments had been tried and failed. This was because of traditional mistrust of earlier cycloablation methods, such as cyclocryotherapy, that were associated with a higher incidence of serious complications than TSCP. As confidence and experience of TSCP grows it is now being safely applied increasingly earlier in the glaucoma treatment paradigm and in eyes with greater visual potential[1]; it has even been suggested that TSCP be used as a one off primary treatment for glaucoma in developing nations with poor access to reliable medical and surgical follow up.

There is still, however, considerable local and regional variation in the use of this treatment (anecdotal impressions suggest that it is used more commonly and earlier for glaucoma treatment in the United Kingdom than in the United States), perhaps in part because of the relative paucity of high quality laboratory and clinical studies demonstrating if, why, and how it is effective. There is even less evidence concerning endoscopic cyclophotocoagulation (ECP), the more refined but less widely available cousin of TSCP.

In the April issue of the *BJO*, Lin *et al* published an important laboratory based study that adds to our understanding of the clinical effects and complications of cyclophotocoagulation (CP).[2] They have attempted to quantify the evolution of vascular changes following CP; their results demonstrate that both TSCP and ECP are associated with an acute occlusive vasculopathy, but that with the endoscopic modality the chronic underperfusion is less than with the transscleral route.

The effects of CP on aqueous secretion are multifactorial. It is widely accepted that a major mechanism of aqueous suppression after CP is coagulative necrosis damage to the secretory ciliary epithelium consequent upon laser energy uptake by the pigmented ciliary epithelium.[3] Further effects are caused by ischaemia; in both TSCP and ECP, some vascular damage occurs as a result of propagation of laser energy from the ciliary epithelium to nearby vessels in the ciliary processes or from tissue disruptions (''pops''), although these

are uncommon in ECP. Tissue disruption may cause collateral damage that compounds the effects of vascular occlusion (which may occur at the level of large or smaller vessels) and variations in clinical efficacy may be in part explained by differences in damage, regeneration, and reperfusion of the ciliary process.

Early forms of laser CP were non-contact, but the development of contact probes that allow conjunctival and scleral compression have reduced the total energy delivery to the eye by allowing more efficient laser delivery with less collateral damage. On the passage of 810 nm diode laser energy through the wall of the eye during TSCP, only about 35% is transmitted to the ciliary epithelium, the remainder being reflected or absorbed.[4] This necessitates higher overall energy delivery in TSCP than ECP and the extra laser absorption may cause further collateral damage in adjacent structures, including blood vessels in the ciliary body or ciliary processes causing potentially widespread ischaemic damage to ciliary epithelium. The evidence of the study by Lin *et al* supports the assertion that ECP is a gentler and less invasive treatment than TSCP.[2] This does not mean that the efficacy of ECP is greater than TSCP (in fact the reverse might be argued) but it does suggest that the incidence of complications might be greater after TSCP than after ECP.

Although it has been previously assumed that the effects of cyclophotocoagulation are on inflow, there is evidence that TSCP may also act as an outflow procedure.[5] This might be explained by damage to the ciliary body that renders it ''leaky,'' promoting an increase in non-conventional outflow, in a manner similar to that seen with the ocular hypotensive action of prostaglandin analogue glaucoma medications. Furthermore, it is reported that aggressive forms of ciliary ablation can cause cyclodialysis clefts, and it is possible that some of the effects of more gentle forms of ciliary body treatment are also caused by small ciliary clefts. Clearly, any outflow effects would compound the comparison between TSCP and ECP. Although a heavy endoscopic treatment might be held to affect outflow if an aggressive burn propagated the process to burn the ciliary body and ciliary muscle, the ability to view the treatment and to stop the propagation of laser energy before it reaches these tissues means that this is less likely to occur.

Most clinical studies of CP in humans have demonstrated a marked initial drop in intraocular pressure (IOP) over the first week, followed by a period of equilibration with rising IOP and stabilisation usually by 1 month after treatment. This may be due to uveitis, vascular damage, and consequent effects upon the blood-aqueous barrier; it is possible that some of the longer term effects of CP may also be due to a similar mechanism, and that the ''drift'' in IOP control may result from vascular repair or reperfusion.[6] The evidence of the current study adds to our understanding of these issues.

> There is no current clear efficacy evidence in favour of endoscopic cyclophotocoagulation over transscleral cyclophotocoagulation, although endoscopic cyclophotocoagulation appears to be associated with fewer complications

There have been some suggestions that CP may be followed by ciliary epithelial remodelling, although it is not known whether regenerated ciliary epithelium is capable of functional aqueous secretion. It may be hypothesised that as ECP has been shown to be less destructive than TSCP, ECP might be followed by a greater amount of functional regeneration of the targeted tissue, as opposed to a complete necrosis following TSCP; this may explain variations in clinical efficacy following different methods of CP, differences in complication rates, and may inform therapeutic decisions such as strategies for re-treatment.

The whole rationale of laser and surgical inflow treatments for glaucoma has been questioned in the past. It has been argued that because glaucoma is an outflow disease it makes little sense to utilise treatments that reduce inflow, at least in the early stages when a more logical approach is to treat the cause by increasing outflow. Traditionally, cycloablation has been reserved for end stage eyes with advanced glaucoma, in which conventional outflow is usually substantially reduced or non-existent and inflow is often also reduced (although as the predominant effect is that on outflow, the overall effect is of raised IOP). It is not rational to wait for advanced disease before further trying to disturb what has by then become a knife edge balance.[7] A more logical paradigm might be to treat moderately advanced glaucoma by a ''safe'' inflow strategy (such as CP), perhaps after failing one or two drainage surgeries but before more aggressive outflow surgery such as glaucoma drainage device (GDD or ''tube'') surgery. Opinions on this remain divided because of the paucity of evidence in favour of either approach.

One large controlled study that compared ECP with GDD (Ahmed valve) surgery in advanced glaucoma showed no differences in efficacy at a mean follow up of some 20 months, although the endoscopic treatment appeared initially more effective and was associated with fewer complications.[8] However, it should be noted that this study applied ECP at pars plana vitrectomy, whereas most practitioners employing ECP do so via a limbal clear corneal approach which can be performed more quickly and usually without the need for a vitrectomy. The different angle of approach upon the ciliary body and processes may account for greater efficacy of the pars plana as opposed to the limbal approach. A logical strategy would be to perform initial ECP treatments through the easy anterior approach and to reserve the pars plana approach for re-treatments or more complex cases, reducing the possible complications of pars planar vitrectomy including vitreous haemorrhage and retinal detachment.

No rigorous scientific studies have been reported directly comparing CP with conventional glaucoma drainage surgery such as trabeculectomy. Nor would it be appropriate retrospectively to compare previous studies of CP with those of conventional mainline surgical strategies, because of marked differences in selection criteria for these two treatments. Clearly, it would be misleading to compare results of CP treatment in these end stage eyes that have undergone (and failed) many previous treatments, with those such as primary trabeculectomy in whom a higher success rate would be expected.

Reservations against previous forms of cycloablation are largely the result of fear of phthisis or hypotony and it is commonly held that such complications are caused by total ciliary epithelial ablation. This appears unlikely in view of clinical observations made at endoscopic treatment after previous forms of CP (including TSCP), demonstrating that many of the ciliary processes had been left completely untreated, and in view of histopathological studies of enucleated human eyes following TSCP showing that the treatment had often completely missed the pars plicata.[3 9] This probably happens because of difficulties with localisation of the ciliary processes, especially in eyes that have undergone multiple previous surgeries.

With ECP the processes are treated under direct vision (preventing undertreatment) and to a visible end point (preventing overtreatment). Despite this advantage, there is no current clear efficacy evidence in favour of ECP over TSCP, although ECP appears to be

associated with fewer complications.[10 11] Lin and co-workers, in their study, postulate that persistence of vascular occlusion after TSCP may correlate with a greater risk of hypotony with this procedure than with ECP.[2] In fact, it is probable that hypotony following CP is multifactorial and the result of a number of causes including ciliary epithelial ablation, anterior segment ischaemia, and the advanced nature of the disease; phthisis is one of the possible outcomes in the natural history of end stage glaucoma, especially secondary glaucomas such as neovascular glaucoma.

The elegant study published by Lin *et al* in the *BJO* provides laboratory data that add substantially to the evidence base needed to explain the mechanism of efficacy and complications in TSCP and ECP and to inform our choice of which treatment is most rational in each complicated clinical setting. Clearly, further laboratory and clinical evidence is needed of the mode of action of these treatments and of their clinical effectiveness; this is especially the case if they are to be used instead of traditional methods of glaucoma drainage surgery, and to be widely accepted as safe and effective earlier than hitherto in the glaucoma treatment paradigm.

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