An update in the management of idiopathic macular hole

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Acknowledgment
Supported in part by the Mr I.K. Ho Foundation, Hong Kong, China.

Key words: Macular hole, Adjunct, Chemical vitreolysis

Introduction

Macular holes are characterized by the absence of neurosensory retinal tissue at the fovea. Clinical interest in macular holes has evolved rapidly during the past decade. In the past, this was a restricted area, even for vitreoretinal specialists, and the disease was categorized as an untreatable blinding disorder. However, the advent of a new classification and hypothesis on the pathogenesis, a better understanding of the natural course of the disease, and the availability of different modalities of treatment have made macular hole an attractive subject for both researchers and clinicians. Recent research into macular holes illustrates the evolution of scientific knowledge and the importance of innovative ideas and surgical techniques in pushing clinical medicine to a new frontier.

Anatomic considerations

The diameter of the macula is approximately 5 mm and, histologically, it contains two or more layers of ganglion cells. The fovea is defined clinically by the annular light reflex off the internal limiting membrane (ILM), and is about 1500 μm in diameter. The central depression in the fovea, devoid of ganglion cells, is the foveola, which has a diameter of about 500 μm.

In the corpus vitreum, collagen fibrils interweave with networks of hyaluronan, which are linked together by glycoprotein. More than 80% of the collagen fibrils are composed of type II collagen while the other constituents include mainly a hybrid of type V/XI and type IX collagen.1,2

The ILM is a basement membrane of Müller cells and is composed of mainly type IV collagen and glycoprotein. The vitreous cortex consists of densely packed type II collagen fibrils and is adherent to the ILM by the force of various extracellular matrix molecules.3 The degree of vitreoretinal adherence varies with age as well as location in the eye. The attachment of the vitreous to the retina is greatest at the vitreous base, over the retinal blood vessels, at the disc and the macula. Over the macula, the adhesion is stronger at the sites where the ILM of the retina is the thinnest. These sites include the fovea and the foveola, which are of great importance to the development of idiopathic or age-related macular hole.

Pathogenesis

Although early hypotheses concentrated on involutional macular thinning4 and preceding macular cyst formation, the primary role of the vitreous traction is now considered to play an important role in the pathogenesis of macular hole.5 In 1983, Avila et al suspected intravitreal anteroposterior traction to be the cause of macular holes.6 This concept was subsequently replaced in the late 1980s by the Gass hypothesis that the holes were due to tangential traction of the vitreous cortex at the foveolar edges.7 This mechanism is supported by clinical observation of the evolution of macular hole and confirmed by histopathologic study.8 Optical
coherent tomography is a new diagnostic imaging technique which uses scanning diode laser and provides additional data about macular formation. Gaudric et al demonstrated that posterior hyaloid detachment begins around the macula. The anteroposterior forces remain in the attached central hyaloid and results in an intraretinal split evolving into a cystic space, followed by disruption of the outer retinal layer and the opening of the foveal floor.

**Clinical presentation and classification**

Patients with macular holes may complain of blurred central vision, central scotoma, or metamorphopsia. Some patients, however, may be entirely asymptomatic, especially if the involvement is monocular and the progression is gradual. This type of hole is noticed only during routine examination. Idiopathic macular holes occur more in elderly people. Macular holes other than the idiopathic type can also be associated with other ocular diseases such as high myopia, ocular trauma, and diabetic and other vascular retinopathy.

Macular holes have different clinical appearances, which vary according to the size of the hole, location, and chronicity. Gass described a new and now widely accepted classification system for macular holes and their precursor lesions in 1988 and a reappraisal of the biomicroscopic classification and anatomic interpretations in 1995 (Figure 1). At stage 1, a foveal detachment occurs with an absence of or decreased foveal depression. Two types of stage 1 lesions have been described; stage 1A (impending hole) has a central yellow spot, whereas stage 1B (impending or occult hole) consists of a yellow ring secondary to the centrifugal displacement of foveolar retina and xanthophyll. The stage 1B yellow ring enlarges during a period of weeks or months and could progress to a full-thickness macular hole.

A stage 2 lesion is an early full-thickness macular hole, which begins eccentrically at one edge of the yellow ring and enlarges with time. An early hole may be less than 100 µm in diameter. The additional contraction of the prefoveolar vitreous cortex causes a 360° can opener-type tear (Figure 2). The contracted prefoveolar vitreous cortex may be visible as an operculum-like opacity (pseudo-operculum) (Figure 3).

The centrifugal retraction of the foveolar retinal receptors continues until a steady size of 400 µm is reached; this is the stage 3 macular hole. It is generally associated with a rim of subretinal fluid, surrounding cystic retinal edema, and a dramatic drop in visual acuity (VA). Small, iridescent yellow deposits at the base of the macular hole are common and are said to represent lipofuscin-laden macrophages or nodular proliferation of retinal pigment epithelium (RPE) overlying eosinophilic material (Figure 4). Chronic macular holes can enlarge up to 800 µm or more and are sometimes associated with pigmentary atrophy or hyperplasia of the underlying RPE.

A stage 4 lesion is identical to a stage 3 macular hole, but has an associated complete posterior vitreous detachment (PVD) and an anterior displacement of the pseudo-operculum. A syneresis cavity alone, however, should not be confused with a PVD.

**Differential diagnosis**

Epiretinal membrane may simulate a full-thickness macular hole. The other disease entities that may mimic the macular hole include cystoid macular edema secondary to a wide variety of ocular diseases, lamellar macular hole, foveal cyst, and vitreomacular traction.

A careful biomicroscopic examination together with a positive Watzke-Allen test are sufficient for making the correct diagnosis in most cases. Ancillary tests may be helpful in less well-defined conditions. Fluorescein angiography, 50-µm laser aiming beam test, retinal thickness analyzer, and scanning laser ophthalmoscopy have all been used...
to make the differentiation in difficult cases. Optical coherence tomography has a very high-resolution power in providing a 2-dimensional, cross-sectional image of the retina which is particularly helpful for the diagnosis and staging.

Natural history and visual acuity

Study of the natural course of the macular hole and of the unaffected eye is important since the data are helpful in counseling patients and planning future treatment. However, most of the earlier studies on the natural course of macular holes are only retrospective or short-term prospective follow-up studies. Furthermore, different classifications and staging have been used, making interpretation and direct comparison of data very difficult.

In Gass’s series, 10 of 18 eyes (56%) with stage 1 macular hole progressed to a full-thickness macular hole, whereas 8 of 18 (44%) underwent spontaneous PVD and did not progress to a macular hole. Hikichi et al, in their study of the natural outcome for stage 1 macular holes, found that of 27 of 40 eyes with the posterior vitreous fully attached to the macula, nine (33%) developed a full-thickness hole. None of the 13 eyes with PVD progressed to a full-thickness macular hole. The initial median VA of both groups was of 20/30 (20/20 to 20/70) and was comparable. All nine eyes that developed a full thickness macular hole had a decreased VA of two or more lines.

In stage 2 macular holes, Hikichi et al demonstrated that most of their patients (21/25 eyes, 84%) progressed, with enlargement of the macular holes, while the hole remained stable in the remaining four patients (16%) during a median follow-up period of 3 years (1 to 5 years). VA started with a median of 20/60 (20/30-20/200) and lost two or more lines in 17 eyes (68%).

In a multicenter, prospective, randomized trial with a 12-month follow-up period, 14 of 19 eyes (74%) progressed to stage 3 or 4, and three holes closed spontaneously. Equally important was that in the majority of patients, the progression occurred within 6 months of the initial examination.

Stage 3 macular holes enlarged in 32/58 eyes (55%), and remained stable in 26 (45%) during the median follow-up period of 3 years (1 to 5 years). The median VA was 20/200 (20/30-20/400). The VA improved two or more lines for two patients (3%), was stable for 39 (67%), and decreased for 17 (29%).

In stage 4 disease, five of 31 macular holes (16%) enlarged — 25 (81%) remained stable and one (3%) resolved spontaneously. The median initial VA was 20/200 (20/30-20/400). VA improved for three patients (19%), remained stable for 24 (77%), and decreased for four (13%).

In the Eye Disease Case-Control Study (EDCCS), the largest prospective study on the natural history of macular hole, 34% of the 122 eyes with macular holes showed an increase in the size of the hole. The rate of spontaneous regression was only 3%. The visual acuity of 45% of eyes deteriorated by two or more lines during follow-up. This was in contrast to other earlier studies, which showed a stable VA in patients with developed macular holes.

The risk of developing a macular hole in an initially unaffected fellow eye in the EDCCS was 4.3% at follow-up of 3 years or less and 7.1% after 6 or more years of follow-up. In a prospective study conducted at the Moorfields Eye Hospital, an estimated risk of fellow eye involvement was 15.6% at 5 years. Previous retrospective studies reported more variable results, from 0% to 16%.
Surgical interventions for macular hole

Prophylactic vitrectomy for impending macular hole

The idea of performing vitrectomy for a stage 1 impending macular hole came from the poor prognosis of the well-developed full-thickness hole and the better understanding of the pathogenesis in macular hole formation. A multicenter, prospective, randomized clinical trial to test the efficacy of prophylactic vitrectomy on impending macular hole showed progression for 10 of 27 eyes (37%) in the vitrectomy group, compared with 14 of 35 eyes (40%) in the observation group. The study could not reach a meaningful conclusion because of an insufficient number of patients, and was discontinued. The low enrollment rate was probably due to the rarity of encountering the disease at an early stage, the difficulty in making the correct diagnosis at such a stage, and difficulty in convincing patients to accept a random treatment. The results were not able to demonstrate any substantial benefit for the group undergoing vitrectomy. Considering the high risk of postoperative nuclear sclerotic cataract, surgical vitrectomy and cortical vitreous removal may not be warranted for an impending macular hole. Further evaluation is needed before a conclusion may be drawn.

Initial vitreous surgery for full-thickness macular hole

Although spontaneous resolution of macular hole and improvement of VA can occur at all stages of macular hole, it should be emphasized that the great majority of macular holes do not improve; some worsen with time. Stage 2 holes are noted to have the highest risk of VA deterioration, whereas stage 3 and 4 holes are usually already associated with poor vision. Therefore, surgery has a role not only in halting disease progression, but also in closing a full-thickness hole with the possible recovery of some central visual function.

The potential role of vitrectomy to close full-thickness macular holes was first demonstrated by Kelly and Wendel. These authors performed pars plana vitrectomy (PPV), removal of the prefoveal cortical vitreous, peeling of epiretinal membranes, fluid-gas exchange with sulphur hexafluoride (SF₆) and, postoperatively, placed patients in the prone position. In a series of 52 patients with full-thickness macular holes, Kelly and Wendel successfully operated on 30 (58%) of these eyes and an overall improved vision was observed in 42%. Clinicopathologic study of successfully treated macular hole revealed that glial cell proliferation may be the possible mechanism for the hole closure. The photoreceptors adjacent to the healed macular holes appeared normal. Defects in the ILM of the foveal area were also noted.

Macular hole surgery using adjunctive additives

In an attempt to improve the success rates and perhaps to eliminate the need for peeling epiretinal membranes, various tissue adhesives have been employed in the treatment of macular hole. In theory, it is the stimulation of fibroglial proliferation that closes the hole. Generally, these additives are used in conjunction with the same surgical techniques already described and include PPV and fluid-gas exchange.

To date, the most extensively studied adjuvant is transforming growth factor-β (TGF-β). Glaser et al achieved an initial exciting result of a 100% macular hole closure rate in 23 patients treated with bovine TGF-β₂ ≥ 330 ng. Thompson et al achieved a 97% success rate in the anatomical closure of macular hole in 36 of 37 eyes with adjuvant TGF-β₂, PPV, and perfluoropropane (C₃F₆). In a subsequent prospective, randomized, placebo-controlled trial of recombinant TGF-β₂, the result was inconclusive as there was no statistically significant difference in the successful closure of macular holes between the groups. Further investigations in this area have been suspended.

Biological tissue glue, a commercially available bovine thrombin plus autologous plasma or cryoprecipitate achieved anatomical success rates of 81% and 77%, respectively, in two non-randomized studies. However, in controlled pilot studies, the treatment benefit has not been shown. Of concern, are the sterile hypopyon and intraretinal hemorrhage that develop following the use of bovine thrombin.

Serum contains only a very low concentration of TGF-β₂, but the possibility of other favorable bioactive cytokines or growth factors makes this a potential adjunctive agent. Liggett et al found 100% anatomic success in 11 eyes treated with human autologous serum as an adjuvant to PPV and gas tamponade.

Minihan et al reported a 96% (48/50) anatomic success rate, using autologous platelet concentrate (APC). Gaudric et al reported a 95% anatomical success rate in 20 eyes. APC has also been tested in a randomized trial of 104 patients with stage 3 or 4 idiopathic full-thickness macular holes. The anatomical success rate in the platelet group was 98% compared with the control group of 82%, although postoperative visual acuity was not significantly different between the two groups at any time. Any conclusion as to the efficacy of these agents is still limited by the lack of large scale, randomized, controlled trials.

Recent macular hole surgery without additives

The initial results using additives are encouraging, but most preparations have not been tested in prospective, controlled, randomized trials. Case selection of shorter duration and better preoperative VA may enhance the success rates in some series. Thus, the attributable benefits of the additives studied have not been well proven. Moreover, the cost of adjuvant therapy, exposure to blood-borne viral pathogens from donors, and the possibility of bacterial contamination during collection of autologous serum should be considered.

With the refinement of instruments and modifications of surgical techniques for the removal of preretinal tissue,
postoperative flattening of the hole can be achieved for more than 90% of patients without the use of adjuncts. Improved success is also a reflection of earlier intervention, better patient education, and positional compliance during the postoperative period.

Removal of internal limiting membrane

A modification of conventional surgery involving removal of the ILM has a higher anatomic and functional success rate. The hypothesis is that the retina around the macular hole may become more mobile or flexible, allowing easier closure of the hole. Rice reported anatomical closure in 123 of 126 eyes (98%) in the group having ILM removal compared with 21 of 30 eyes (70%) in the group treated without ILM removal. Park et al reported an overall anatomical success rate of 91% from primary surgery with ILM peeling in their series of 58 consecutive eyes. For the group of patients with a symptom history of less than 6 months’ duration, the results were 98% versus 69% for those with more than 6 months’ history.

Eckardt et al demonstrated 92% closure of the holes in their series of 39 eyes. ILM can be removed by various techniques using specially designed instruments. ILM is distinguished from the epiretinal membrane by its typical characteristics of transparency, uniform thinness, tendency to scroll, and absence of elasticity. After its removal, the exposed surface of the retinal nerve fiber shows mild whitening and further suction or manipulation may produce a fluffy appearance or even bleeding from the retinal vessels. The salient features of ILM, including Müller cell processes and canals leading from the inner to the outer surface, can be shown by electron microscopy.

Laser photoocoagulation in macular hole surgery

Schocket et al treated 18 patients with macular holes by argon green laser to the rim of the hole. The 50 or 100 μm spot size laser applications were made to the temporal 270° or the entire circumference around the hole and the power ranged from 50 to 250 mW. The aim was to clear the subretinal fluid rather than to close the hole. 10 eyes (55.6%) improved three to eight lines, five eyes (27.8%) remained the same, and the vision of three (16.6%) deteriorated three to five lines. However, this method was heavily criticized as the initial favorable result may not be sustained due to laser-induced atrophic changes in the RPE. More recently, the successful management of recurrent macular holes by photocoagulation to the base of the hole together with a fluid-gas exchange has been reported. Min et al reported a series of eight consecutive patients with idiopathic macular holes treated with endolaser to the base of the hole together with PPV, epiretinal membrane peeling, and fluid-gas exchange. All patients achieved anatomical closure of the hole and improvement in VA of three lines or more. Laser photocoagulation to the base of the hole may be a useful adjunct but requires further investigation and long-term evaluation.

Gas tamponade and head positioning

Following complete PPV, options for intraocular tamponade include air, SF₆, C₃F₈, or silicone oil. In the study by Wendel et al, 125 of 170 macular holes (73%) were successfully closed with the use of a nonexpansile mixture of SF₆. More recently, Glaser et al showed successful hole closure in > 90% of patients using C₃F₈. Thompson et al have reported anatomic success in 53% of patients for whom air was used compared with 97% who were given 16% C₃F₈.

Theoretically, the use of long-acting gases may provide better hole tamponade in patients who are less compliant with strict face down positioning. The problems with these gases, however, include an increased risk of cataract formation and slower visual recovery. A face-down position for 2 to 4 weeks is recommended for most patients, although one study reported a 79% anatomic success without face-down positioning. For patients who are less compliant with this position, use of silicone oil or combined surgery with cataract extraction are suggested for selected cases.

Silicone oil in the treatment of idiopathic macular hole

Silicone oil tamponade may be considered for patients who are unable or unwilling to assume a face-down position, as the patient can return to near normal activity immediately. Unlike intraocular gas, the vision is less affected in the postoperative period and there is no restriction on air travel.

The force of tamponade by silicone is less than that of an intraocular gas and the rate of success depends on the surface tension and the completeness of filling of the silicone oil. The 40 eyes in the Goldbaum series, 32 (80%) sealed after a single operation and an additional five sealed after the second procedure (93%). The results were comparable with vitrectomy using long-acting gas.

The disadvantages in using silicone oil include the need for a second procedure to remove the oil, a higher total expense, and complications secondary to the use of silicone oil. The rate of macular hole reopening after removal of the silicone oil has been reported to be 20%, which is higher than the rate of spontaneous re-opening in the other reported series.

Treatment of persistent or reopened macular holes

Incomplete cortical vitreous peeling may result in postoperative failure in closure of macular hole for some patients, while poor compliance with posture during the postoperative period may be important for others. Macular holes of longer duration also relate to a higher failure rate in the anatomic closure.

Re-operation with rigorous epiretinal membrane dissection, autologous serum, and long-acting gas tamponade appear to allow the closure of most macular holes. For those patients,
unwilling or unsuitable for a second operation, laser photocoagulation to the foveal pigment epithelium followed by fluid-gas exchange can be an effective alternative.\textsuperscript{43,44,54}

Prognostic factors and visual outcome

The large variability in VA outcomes after surgery may be due to the different pre-operative baselines, complications of surgery, and the progression of cataract. Favorable predictors for both anatomic and visual success include early stage of the disease, good pre-operative vision, short duration of symptoms, and small size of the holes.

Ryan and Gilbert have reported one of the largest series of stage 2 macular holes treated with PPV within 6 months of the onset of symptoms.\textsuperscript{55} They were able to achieve an overall anatomical success rate of 94% (34 of 36 eyes). In their series, 72% of stage 2 patients attained a final visual acuity of 20/40 or better, compared with only 58% of patients with stage 3 or 4 holes. In comparison, in the series by Wendel \textit{et al.}, 20/40 or better vision was obtained only in 29% with stage 3 and 4 holes.\textsuperscript{46}

Results of a multicenter, randomized, clinical trial to compare the risks and benefits of standard macular hole surgery with observation demonstrated that the benefits of the surgery exist not only in anatomic closure of the hole, but also in the visual outcomes.\textsuperscript{56}

Roth \textit{et al} reported that treatment of chronic macular holes had a similar anatomical success rate, but a poorer visual prognosis than acute holes after surgery.\textsuperscript{57} Five of 11 eyes (45%) with chronic holes had a final visual acuity of two lines improvement compared with 8 of 11 (73%) in the acute presentation group.\textsuperscript{58} Thompson \textit{et al} reported that in chronic macular holes of longer than 2 years duration (mean, 3.7 years), the success rate of anatomical closure was as low as 32 of 51 eyes (62.7%) and only 21 eyes (46.7%) gained 3.7 years), the success rate of anatomical closure was as low as 32 of 51 eyes (62.7%) and only 21 eyes (46.7%) gained 3.7 years), the success rate of anatomical closure was as low as 32 of 51 eyes (62.7%) and only 21 eyes (46.7%) gained 3.7 years), the success rate of anatomical closure was as low as 32 of 51 eyes (62.7%) and only 21 eyes (46.7%) gained 3.7 years), the success rate of anatomical closure was as low as 32 of 51 eyes (62.7%) and only 21 eyes (46.7%) gained 3.7 years), the success rate of anatomical closure was as low as 32 of 51 eyes (62.7%) and only 21 eyes (46.7%) gained 3.7 years), the success rate of anatomical closure was as low as 32 of 51 eyes (62.7%) and only 21 eyes (46.7%) gained

In summary, chronic macular holes of longer than 2 years duration (mean, 3.7 years), the success rate of anatomical closure was as low as 32 of 51 eyes (62.7%) and only 21 eyes (46.7%) gained 3.7 years), the success rate of anatomical closure was as low as 32 of 51 eyes (62.7%) and only 21 eyes (46.7%) gained 3.7 years), the success rate of anatomical closure was as low as 32 of 51 eyes (62.7%) and only 21 eyes (46.7%) gained 3.7 years), the success rate of anatomical closure was as low as 32 of 51 eyes (62.7%) and only 21 eyes (46.7%) gained 3.7 years), the success rate of anatomical closure was as low as 32 of 51 eyes (62.7%) and only 21 eyes (46.7%) gained 3.7 years), the success rate of anatomical closure was as low as 32 of 51 eyes (62.7%) and only 21 eyes (46.7%) gained 3.7 years), the success rate of anatomical closure was as low as 32 of 51 eyes (62.7%) and only 21 eyes (46.7%) gained 3.7 years), the success rate of anatomical closure was as low as 32 of 51 eyes (62.7%) and only 21 eyes (46.7%) gained 3.7 years), the success rate of anatomical closure was as low as 32 of 51 eyes (62.7%) and only 21 eyes (46.7%) gained.

Other outcomes and complications

Spontaneous late re-opening of macular holes after initially successful treatment with vitreous surgery was observed in eight of 167 eyes (4.8%) after 2 to 22 months; all were associated with an acute drop in vision.\textsuperscript{51} The growth of a preretinal membrane around the holes played a role in the re-opening. Re-operation could give a good second anatomical success with subsequent visual improvement to 20/50 or better.\textsuperscript{51} Another report on the rate of late opening by Park \textit{et al} was 2%.\textsuperscript{52}

The risk of macular holes re-opening may be further increased if a second procedure is to be performed. Goldbaum \textit{et al} found that the macular hole re-opened in 20% of patients undergoing a second procedure of silicone oil removal.\textsuperscript{48} If cataract surgery was performed as a subsequent procedure, the risk of re-opening may be increased to 16%.\textsuperscript{60}

Patients undergoing macular hole surgery are exposed to the same risks and possible complications as patients having vitrectomy for other indications. Progression of nuclear sclerotic cataracts is a known complication, especially for elderly patients. With the use of long-acting gases for tamponade, a greater risk for cataract progression is anticipated. Thompson \textit{et al} found that nuclear sclerotic cataracts progressed in 75% of eyes by 1 year and in 95% of eyes followed for 2 years.\textsuperscript{61} Posterior segment complications, including peripheral retinal breaks, retinal detachment, photic toxicity, and endophthalmitis, were noted in 23 of 98 eyes (23%).\textsuperscript{52}

Visual field loss after otherwise successful surgery for macular holes is an unexpectedly common and serious complication. The reported incidence varies from 7 to 23%.\textsuperscript{62-64} The visual defects may be wedge-shaped, altitudinal, baring of the blind spot, and are more common in the inferotemporal and inferonasal quadrants.\textsuperscript{62,64} Although unclear, the etiology may involve mechanical trauma to the peripapillary retinal vasculature or nerve fiber layer during PVD induction or fluid aspiration.\textsuperscript{62} Another possibility includes retinal damage caused by the flow of dry room air during gas-fluid exchange.\textsuperscript{55}

Combined surgery with cataract extraction

Thompson \textit{et al} pointed out the high percentage of patients who develop cataract after macular surgery.\textsuperscript{61} Use of long-acting gas exacerbates the progression of cataract. However, using a long-acting gas is an important element for success. So, a combined operation of macular surgery with phacoemulsification and intraocular lens implantation could be a feasible surgical option.\textsuperscript{66,67} In the absence of the risk of developing cataract, patients may be less stringent in adopting the face-down position.\textsuperscript{69} They have better long-term visual outcomes and are not exposed to a risk of macular hole re-opening secondary to subsequent cataract extraction. However, the possible downside of combined surgery, including cystoid macular edema (CME), should also be addressed. Sheidow \textit{et al} reported the incidence of CME in three of seven patients in the combined surgery group and one of 15 in the consecutive vitrectomy and phacoemulsification group.\textsuperscript{67} The incidence and pathogenesis of CME must be further investigated.

Development of chemical vitreolysis

Gass implicated that prefoveal cortical vitreous traction caused macular holes and suggested the beneficial role of surgical induction of a PVD by vitrectomy.\textsuperscript{7} Using a similar analogy, PVD induced by an expansible gas bubble
or chemical agent may abort the progression of macular hole evolution. The study by Chan et al demonstrated that PVD was induced in 18 of 19 eyes without prior PVD within 2 to 9 weeks of a gas injection. Impending macular holes may resolve and some of the stage 2 macular holes may close using this method.

A potential area of development in the management of macular hole is noninvasive pharmacological vitreolysis. The success of these agents depends on their ability to induce a liquefying corpus vitreous (syneresis), leading to the separation of the corpus vitreous away from the retina (syneresis). Diapase is a non-specific enzymatic vitreolysis agent currently under investigation. It has been proven to be effective in inducing PVD in porcine and human cadaver eyes in vitro. Plasmin is another non-specific enzymatic vitreolysis agent which has been used together with SF6 to induce PVD in animal studies. Hyaluronidase is a substrate-specific enzymatic vitreolysis agent. Its efficacy in inducing PVD has been shown following intravitreal injection in rabbits. This is a new but potential area of study and, so far, the results are encouraging. Pharmacological vitreolysis may be considered as an alternative or adjunct to conventional mechanical vitrectomy for the management of macular holes in the future.

**Conclusion**

Today’s unthinkable could be tomorrow’s invention. The concepts in the management of full-thickness macular hole have changed dramatically during the past decade. Macular hole is now considered as a treatable disease. Surgery is almost a conventional practice. Since smaller hole and earlier intervention carry better prognosis, prompt referral of patients with macular holes to a vitreoretinal specialist is essential.

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