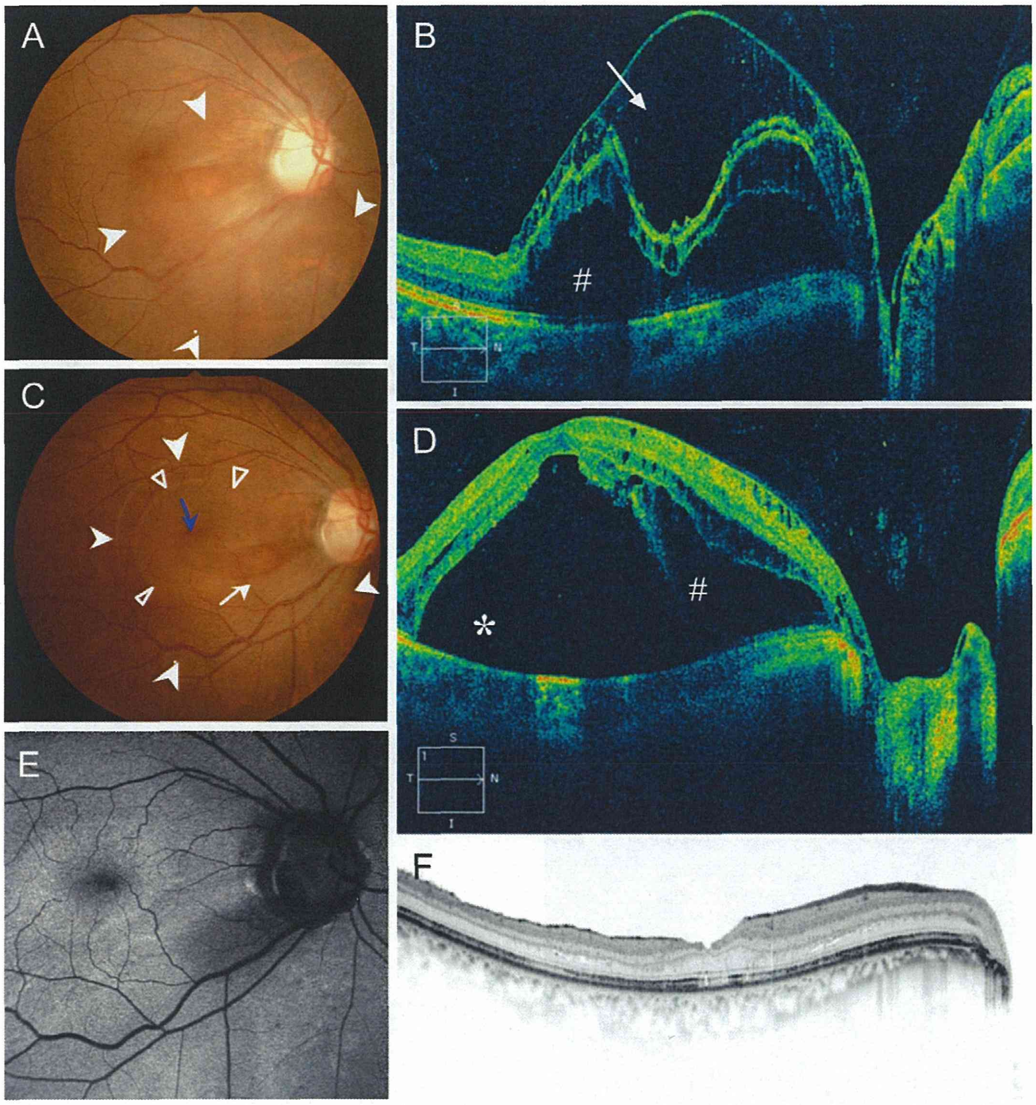
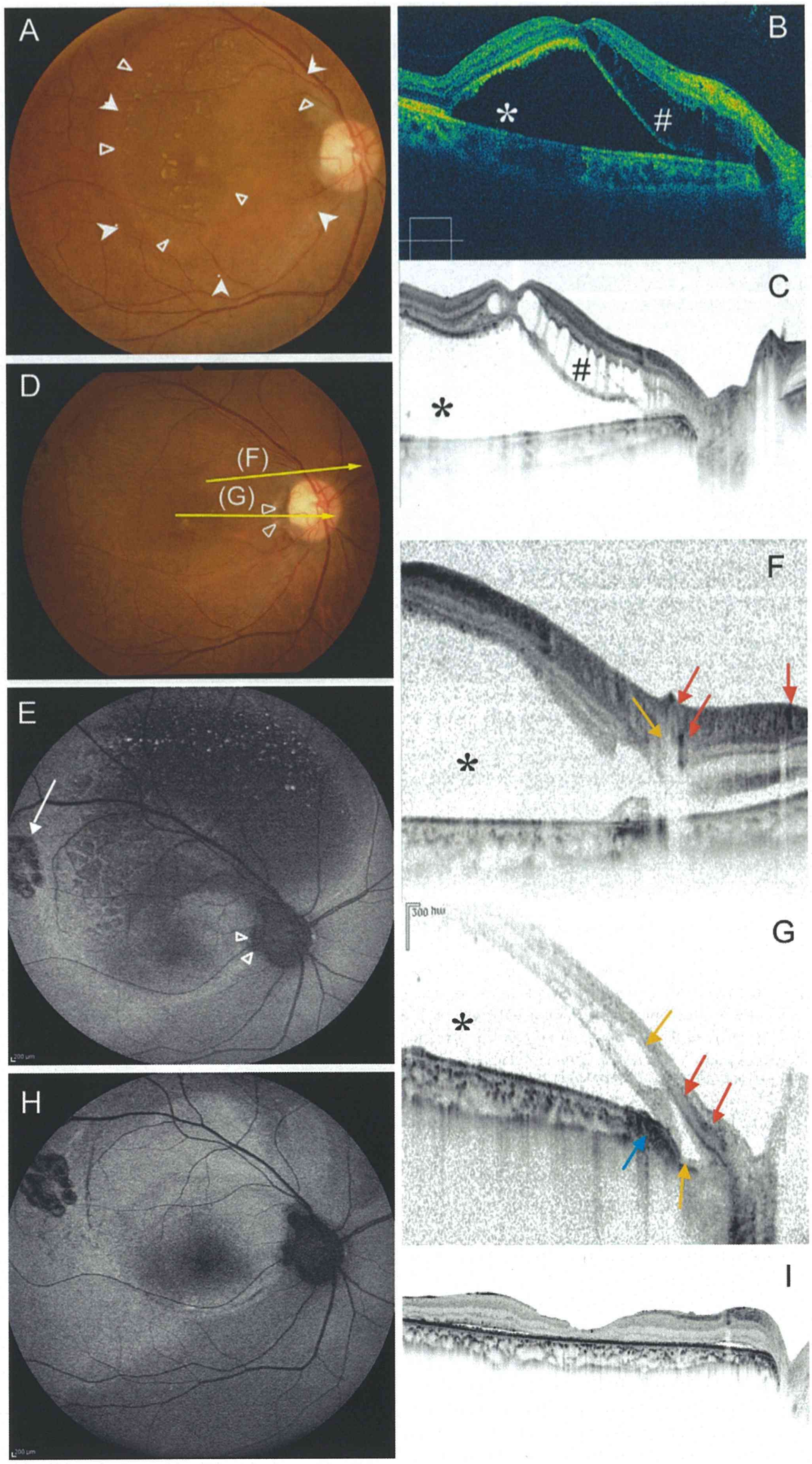


Figure 2. Composite of representative clinical findings from patient 8. **A,** Fundus photograph from the right eye obtained at the initial visit showing an inferotemporal optic disc pit associated with a large, round area of inferotemporal retinal elevation from optic disc (arrowheads). Before surgery, the best-corrected visual acuity (BCVA) was 20/17. **B,** Optical coherence tomography (OCT) scan obtained at the initial visit revealed a multilayered inner retinoschisis-like separation (#) with internal limiting membrane (ILM) detachment (arrow) connected to the optic disc pit. There was not retinal detachment. **C,** Preoperative photograph obtained at 2 months after the initial visit showing enlargement of retinal elevation beyond macula and appearance of round macular detachment (white open arrowheads). Tiny outer retinal break (blue arrows) and small area of shallow retinal with ILM separation (white arrow) were observed. The BCVA decreased to 20/50. **D,** Preoperative OCT scan revealing the development of retinal detachment (*) around the fovea and increased outer nuclear separation (#) with inner multilayers and retinoschisis-like separation between the optic disc and macula. **E,** Fundus autofluorescence image obtained 14 months after vitrectomy showing diffuse faint granular hyperfluorescence at the previous retinal detachment area. The BCVA was 20/20. **F,** Optical coherence tomography scan obtained 14 months after surgery showing improved complete retinal reattachment with tiny defect of the inner segment/outer segment line of the fovea.

Figure 1. Composite of representative clinical findings from patient 7. **A,** Photograph of left fundus before surgery showing a temporal optic disc pit associated with a large, round area of macular detachment (white open arrowheads). After surgery, the best-corrected visual acuity (BCVA) was 20/70. **B,** Preoperative fundus autofluorescence (FAF) image showing hypofluorescence in the area of retinal detachment. **C,** Optical coherence tomography scan obtained before surgery revealing a multilayered inner retinoschisis-like separation with internal limiting membrane (ILM) detachment (white solid arrow) and retinal detachment (*) present from the margin of the optic disc pit. **D,** Optical coherence tomography scan obtained on postvitrectomy day 1 showing a markedly decreased retinal detachment (*) and a shallowing of the retinoschisis-like separation next to the optic disc. The BCVA was 20/200. **E,** Optical coherence tomography scan obtained 6 months after vitrectomy: the retinoschisis-like separation and retinal detachment (*) were much decreased, but the ILM detachment between disc and macula remained (arrow). The BCVA was 20/70. **F,** Fundus autofluorescence image obtained 12 months after vitrectomy showing diffuse granular hyperfluorescence within the area of retinal detachment. **G,** Optical coherence tomography scan obtained 12 months after vitrectomy showing only a persistent shallow macular detachment. The outer segments of photoreceptors were thickening within the subfoveal lesion. Shallow ILM separation (arrow) beside the optic disc remained. The BCVA was 20/70. **H,** Fundus photograph obtained 16 months after surgery showing complete retinal reattachment with a clearer margin of optic disc pit. The BCVA was 20/30. **I,** Fundus autofluorescence image obtained 16 months after surgery showing fine granular hyperfluorescence at the site of previous retinal detachment. **J,** Optical coherence tomography scan obtained 16 months after surgery showing improvement in outer retinal anatomic features with a persistent defect in the inner segment/outer segment line at the fovea.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reattachment (Figs 1 and 2). The degree of excavation of the pits was not obvious before surgery; however, after surgery as the retina reattached, the pits were observed easily as being darker and deeper compared with the surrounding areas. The OCT images confirmed the increased depth of the excavation at the optic disc pit after vitrectomy in patients 1 and 7. Even after complete retinal reattachment, fine ILM elevation beside the optic disc remained in some eyes.

Visual Acuity Results

Preoperative and final BCVA are shown in Table 1. Despite evidence of some residual shallow schisis-like separation and some persistent macular detachment, the BCVA started to improve within a few months in all 7 successful eyes. This generally corresponded with reduced macular elevation and a better appearance of the photoreceptor outer segments on OCT. All eyes with retinal reattachment, except for patient 6 who needed additional treatment, had a postoperative BCVA of 20/30 or better. Although 3 eyes had a postoperative BCVA of 20/20 or better, a mild central scotoma or metamorphopsia remained. The BCVA of 1 eye (patient 6) started to improve after additional laser therapy and eventually reached 20/50.

Fundus Autofluorescence Findings

The FAF findings were obtained both before and after surgery in 3 eyes (patients 6, 7, and 8) and only after surgery in 1 eye (patient 4). Preoperative FAF images showed a prominent hypofluorescence corresponding to a high retinoschisis-like separation or macular detachment and a slight hypofluorescence corresponding to a shallow retinoschisis-like separation. After surgery, there was an increase in granular hyperfluorescence in FAF images accompanied by an increase in the amount of subretinal precipitates (Figs 1 and 2). This corresponded to a thickening of photoreceptor outer segments on OCT. Even after complete retinal reattachment, hyperfluorescence at the site of previous retinal detachment persisted through the most recent visit. In patient 6, the FAF images demonstrated an increase in granular hyperfluorescence with reduction of macular detachment after additional laser treatment (Fig 3).

Discussion

In this study, induction of a PVD without a gas tamponade seemed to be as effective as doing the same with a gas tamponade.[16] Optical coherence tomography revealed a reduction in the abrupt retinal elevation adjacent to the optic disc as well as a decrease in the inner retinoschisis-like separation in the early postoperative period. After reduction of the retinoschisis-like changes, there was a slow decrease in the macular retinal detachment, with complete resolution in 7 of 8 eyes within 16 months (average, 12 months; Figs 1 and 2). This pattern of improvement of macular elevation is similar to what was noted in a previous treatment using a gas tamponade.[16]

Bonnet[18] previously reported that none of the eyes with macular detachment in her series had evidence of a PVD and that the 2 eyes that demonstrated spontaneous reattachment did so after a PVD developed. In addition, Theodossiadis et al[19] described vitreous abnormalities such as vitreomacular traction and vitreous strands over the optic disc associated with optic disc pit maculopathy. In the current series, the sharp retinal elevation adjacent to the optic disc and inner retinoschisis-like separation immediately decreased after surgery, suggesting that traction on the peripapillary retina may be a trigger of optic disc pit maculopathy. Vitreoretinal traction is an important factor in the pathogenesis of optic disc pit maculopathy.

Recent advancements in OCT technology show that retinoschisis-like retinal separation is most prominent in the outer nuclear layers and frequently is combined with multiple shallow inner retinal separations.[19–21] A prominent elevation of the ILM has been reported in some eyes,[20] and a large, spontaneous separation of the ILM was observed before surgery in 1 eye (patient 8) in the current series. After surgery, shallow ILM detachment adjacent to the optic disc remained after complete retinal reattachment in some eyes. Similar to the original hypothesis of Lincoff et al,[5] in some, eyes schisis-like retinal separation preceded frank macular detachment with reduced vision.

Internal limiting membrane removal was performed in only 1 eye in this series. That eye (patient 8) had a spontaneous ILM detachment at presentation. There are some reports suggesting that ILM peeling is indicated during vitrectomy for optic disc pit maculopathy.[22–24] Internal limiting membrane removal ensures complete hyaloid removal. A partially separated ILM or ILM with cellular proliferation on its surface may contribute to peripapillary traction. Mac-

Figure 3. Composite of representative clinical findings from patient 6 (unsuccessful case). **A,** Right fundus photograph obtained before surgery showing an inferotemporal optic disc pit associated with a large, round macular elevation connected to the optic disc (large, solid arrows) and higher elevated macular detachment (white open arrowheads). The patient reported metamorphopsia, and the best-corrected visual acuity (BCVA) was 20/25. **B,** Preoperative optical coherence tomography (OCT) scan revealing a high separation of retinal detachment (*) with outer nuclear schisis-like separation (#) and shallow internal limiting membrane elevation connected to the optic disc pit. **C,** Optical coherence tomography scan obtained 12 months after vitrectomy, when the patient reported decreased vision, revealing recurrence of retinoschisis-like separation at the outer nuclear layer (#) and the worsening of retinal detachment (*). The BCVA decreased to 20/50. **D,** Fundus photograph obtained after additional treatment of gas tamponade and drainage of subretinal fluid, which did not work. Gas tamponade and laser photocoagulation were added to a small area beside the vessel in the peripapillary region (white open arrowheads). At 20 months after initial vitrectomy, subretinal fluid moved upward after laser treatment and decrease of macular detachment. The BCVA was 20/70. **E,** Fundus autofluorescence image obtained after the additional treatments at 20 months after initial vitrectomy revealing the laser spots around intentional break for the drainage of subretinal fluid (arrow) and beside the optic disc (white open arrowheads). The area of macular detachment started to increase the hyperfluorescence corresponding to the reduction of macular detachment and enlargement of hypofluorescence at the upper posterior retina corresponding to the high retinal elevation. **F–G,** Optical coherence tomography scan obtained during the follow-up after the additional treatment showing the subretinal space (*) connected to the perivascular space (yellow arrows) beside the retinal vessels (red arrows), especially around the optic disc. Laser scar next to the optic disc pit attached with neural retina (blue arrows). **H–I,** At 7 months after photocoagulation, **(H)** the image of FAF was the increase of hyperfluorescence **(I)** corresponding to macular reattachment by the OCT finding. The BCVA was 20/50.

Table 1. Preoperative Clinical Characteristics

Patient No.	Age (yrs)	Gender	Eye	Refractive Error (D)	Symptom	Preoperative Best-Corrected Visual Acuity	Pit Location	Duration of Symptoms (mos)	Outer Layer Schisis-like Separation
1	41	M	L	−2.75	Central scotoma	20/300	Inferotemporal	35	++
2	12	M	R	0	Decreased BCVA	20/40	Inferotemporal	28	++
3	20	M	L	0	Central scotoma	20/100	Temporal	10	−
4	56	M	L	−5.25	Central scotoma	20/100	Temporal	15	++
5	36	F	L	−1.25	Metamorphopsia	20/40	Temporal	3	++
6	47	F	R	+0.5	Metamorphopsia	20/25	Inferotemporal	18	+
7	8	M	L	−1.0	Decreased BCVA	20/70	Inferotemporal	2	+
8	38	M	R	0	Decreased BCVA	20/50	Inferotemporal	3	++

BCVA = best-corrected visual acuity; D = diopters; F = female; ILM = internal limiting membrane; L = left; M = male; R = right; + = present; ++ = remarkable finding; − = absent.
*Based on only time-domain optical coherence tomography observation.
†After first operation.
‡First, gas tamponade; second, internal limiting membrane peeling + subretinal fluid drainage + gas tamponade; third, laser (application).

ular schisis without an optic disc pit or resulting from high myopia has been reported,[25–29] suggesting that in some cases, vitreomacular traction can cause macular elevation resembling that resulting from optic disc pit maculopathy. The high degree of success noted in this series with careful and complete hyaloid removal as visualized with triamcinolone acetonide, however, suggests that ILM peeling is probably not essential in the treatment of most cases of optic pit maculopathy.

Previously, the authors reported that infrared and fundus autofluorescent images in optic disc pit maculopathy reflect the changes in the schisis-like separation and macular detachment corresponding with anatomic recovery,[30] Similar to Spaide,[31] it was found that FAF images developed brighter areas with increased granular hyperfluorescence corresponding to a thickening of photoreceptor outer segments on OCT after vitrectomy. This hyperfluorescence persisted for an extended period even after complete retinal reattachment. This FAF pattern during resolution of the macular detachment after vitreous surgery is very similar to the FAF images of chronic central serous choriodopathy.[32]

The BCVA started to improve after surgery despite the continued, albeit decreased, presence of schisis-like separation and foveal detachment. Optical coherence tomography images suggested that the main difference in the macular detachment after surgery compared with before surgery was a more regular appearance of the photoreceptor outer segments, corresponding to areas of hyperfluorescence on FAF images. If the source of intraretinal or subretinal fluids derives from the optic disc pit, fluid currents should be necessary to separate the intraretinal and subretinal spaces. Vitrectomy to remove the traction around the entrance cavity may decrease fluid currents and better allow remodeling of photoreceptor outer segments and, ultimately, better visual function.

In 1 of 8 eyes in this series (patient 6), macular reattachment with vitrectomy alone failed. Revision of vitrectomy with ILM peeling and subretinal fluid drainage with gas tamponade was not sufficient to reattach the macula, and local laser treatment to a small area beside the vessel in the peripapillary region was added. This reduced the macular detachment and shifted the subretinal fluid to the superior area around superior arcade. This suggested that the fluid may have come along the vessels from the optic disc into the intraretinal areas. The perivascular space at the optic disc may be connected to the subarachnoid space, just like Virchow-Robin spaces in the brain,[33] and the eyes with optic disc pit maculopathy may have enlarged perivascular spaces. The fluid flow around the perivascular space is consistent with the induction of a dome-shaped ILM elevation in patient 8 and in previously reported cases.[20,23]

Histopathologic analysis of optic disc pits reveals perineural herniation of poorly differentiated retinal tissue combined with vitreous collagen around the optic nerve into the subarachnoid space.[34] In our cases, vitrectomy with induction of a PVD led to deepening of the excavation of the pit. There may be transparent neural tissue in the pit separating the vitreous cavity from the subarachnoid space.[35] The pit is porous because of the disorganized tissue, and the lamina cribrosa also is defective within the pit.[34] Intracranial pressure and intraocular pressure both fluctuate, although intraocular pressure is usually greater than intracranial pressure. When intraocular pressure is greater, vitreous fluid moves into the pit sac. When intracranial pressure is greater, depending on the body position, for example, some fluid in the sac may be pushed back into the eye through the pit. However, some fluid in the sac also could move into the retina, leading to a retinoschisis-like separation. The authors believe that this dynamic fluid movement in the pit sac like is an eddy where there is turbulent flow. The turbulent flow contributes to the enlargement of the pit sac or perivascular spaces and is the cause of the schisis-like separation. When there is posterior hyaloid traction caused by age-related vitreous liquefaction or trauma, it pulls on the optic disc pit. Because the pit is pulled up like a tent by vitreous traction, the turbulent flow may have increased access around the vessels to the intraretinal space. This traction affects the peripapillary retina, especially around the pit. This further facilitates intraretinal fluid accumulation. When a PVD occurs, the anterior traction is released. The pit decompresses and moves downand Outcomes of Vitrectomy

Inner Layer Separation	Retinal Detachment	ILM Detachment	Outer Layer Break	Posterior Vitreous Detachment	Time to Macular Attachment (mos)	Additional Treatment	Most Recent Best-Corrected Visual Acuity	Follow-up (mos)
–*	+	–	+	–	14	–	20/17	35
+	++	–	+	–	10	–	20/17	46
–	+	–	–	–	10	–	20/30	10
+	+	–	+	–	15	–	20/30	35
–*	–	–	–	–	6	–	20/25	18
+	++	–	–	–	24†	+(3 times)‡	20/50	24
+	++	+	–	–	16	–	20/30	20
+	+	+	+	–	12	–	20/20	16

ward, and access to the subretinal space becomes limited. Any traction on the peripapillary retina also is released.

During induction of a PVD, a tight adhesion of the posterior hyaloid or abnormal membrane, such as anomalous Cloquet's canal, to the margin of the disc pit has been reported.[36,37] The authors have observed during surgery a posterior hyaloid strand tightly attached to the optic disc pit using triamcinolone acetonide that was sucked into the pit as a PVD was created,[36] suggesting that the unusual movement of fluid between the vitreous cavity and subarachnoid space and traction around the posterior hyaloid may contribute to the pathogenesis of this disease.

In conclusion, vitrectomy with induction of a PVD without a gas tamponade or laser photocoagulation allows resolution of optic disc pit maculopathy in most cases. Treatment without a gas or silicone oil tamponade avoids intraoperative and postoperative complications related to the tamponading agent.[16,38,39] This study suggests that peripapillary vitreous traction is the trigger of the schisis-like separation and that the perivascular space around the optic disc pit allows for the passage of fluid into the retina associated with optic disc pit maculopathy.

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Low-Frequency Subthalamic Nucleus Stimulation in Parkinson's Disease: A Randomized Clinical Trial

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ABSTRACT

Background: Low-frequency, bilateral stimulation of the subthalamic nucleus can improve axial symptoms of advanced Parkinson's disease (PD), but it is not particularly effective for segmental symptoms.
Methods: The optimal contacts for low-frequency (60 Hz) and high-frequency (130 Hz) single monopolar stimulation were determined. Then, in a randomized, double-blind, prospective crossover manner, 60-Hz and 130-Hz stimulations via the respective optimal contacts were compared for immediate efficacy in improving the motor function of patients with PD.
Results: The optimal contacts for 60-Hz stimulation were situated more ventrally than those for 130-Hz stimulation ($P = 0.038$). Under the respective optimal, single monopolar stimulation, 60 Hz provided superior efficacy over 130 Hz in improving the total Unified Parkinson's Disease Rating Scale motor score ($P < 0.001$) and the akinesia ($P = 0.011$) and axial motor signs ($P = 0.012$) subscores without compromising the therapeutic effect on tremor and rigidity.
Conclusions: Low-frequency stimulation via the optimal contacts is effective in improving overall motor function of patients with PD. © 2014 International Parkinson and Movement Disorder Society
Key Words: Parkinson's disease; deep brain stimulation; subthalamic nucleus; low-frequency stimulation; motor function

Subthalamic nucleus (STN) deep brain stimulation (DBS) is a well-established treatment aimed at controlling motor symptoms of Parkinson's disease (PD). Over the long term, however, axial symptoms (gait, postural stability, and speech) worsen in 60% to 80% of patients treated by STN-DBS.[1] Recent studies have suggested that STN stimulation at relatively low frequency (ie, 60-80 Hz) may be beneficial in controlling axial symptoms that continue to deteriorate under high-frequency stimulation.[2-5] However, findings regarding the effect on segmental symptoms (tremor, rigidity, and bradykinesia) have been somewhat inconsistent. Although it has been reported that the dorsal STN is the ideal target for high-frequency STN-DBS,[6,7] ventral contacts were used in the majority of patients in a study that reported satisfactory effects with low-frequency 60-Hz STN stimulation.[2] These observations prompted us to postulate that the optimal contact sites differ for high-frequency stimulation and relatively low-frequency stimulation. In a single-center, randomized, double-blind, crossover study, we tested the efficacy of relatively low-frequency stimulation via its optimal contacts for improving overall motor function of patients with PD who were treated with bilateral STN-DBS.

Patients and Methods

The study was conducted in 2 stages. Stage 1 was a double-blind study performed before randomization to determine the optimal contacts for each of the relatively low-frequency 60-Hz stimulation and the high-frequency 130-Hz stimulation. Optimal contacts were defined as single monopolar contacts that yielded the best Unified Parkinson's Disease Rating Scale motor examination (UPDRS-III) score. Stage 2 was a randomized, double-blind, crossover study to assess the immediate effects of 60-Hz and 130-Hz stimulation via the respective optimal contact sites (hereafter called *optimal-60-DBS* and *optimal-130-DBS*, respectively). Patients were randomly assigned to undergo assessments in 1 of 2 treatment sequences. In sequence A, patients were treated under optimal-130-DBS for 1 hour. After the first evaluation, the treatment condition was changed to optimal-60-DBS, and a second evaluation was conducted 1 hour later. In sequence B, the order of the treatment condition was reversed (Supporting Fig. 2). For a detailed description of the

Additional Supporting Information may be found in the online version of this article.

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TABLE 1. Results of analysis of test scores under optimal-60-DBS and optimal-130-DBS

Outcome Measures	Maximum Possible Score[a]	Optimal-130-DBS	Optimal-60-DBS	Carry-Over Effect: *P* Value	Difference[b]	*P* Value
Primary outcome measure: Mean ± SD[c]						
UPDRS-III total score	108	16.0 ± 6.9	11.4 ± 7.2	0.603	4.6 ± 4.0	< 0.001[d]
Secondary outcome measures: Median [IQR][e]						
UPDRS-III subscores						
Axial motor signs	16	4.5 [1.5-5]	3.5 [1-4]	0.825	1 [0-1]	0.012[d]
Akinesia	32	7 [5.25-9]	7 [2-6.5]	0.153	2 [1.25-4]	0.011[d]
Tremor	28	0 [0-1]	0 [0-1]	0.368	0 [0]	1.000
Rigidity	20	2 [2-3.75]	2 [2-2.75]	0.387	0 [0-1]	0.214
Timed 10-meter walk test						
Completion time(s)	—	9.5 [8.6-10.9]	9.3 [8.5-10.3]	0.755	0.7 [0.2-1]	0.006[d]
No. of steps	—	19 [18-23]	19 [16-22]	0.755	1 [0.5-1.5]	< 0.001[d]
Freezing of gait	—	0 [0]	0 [0]	—	0 [0]	—
Berg Balance Scale[f]	56	50 [46.5-52]	51 [49-55]	0.918	1.8 [0-2.4]	0.062

[a]Higher scores on the Berg Balance Scale represent better function. Higher scores on all other items represent worse function.
[b]The differences between scores under optimal-130-DBS and optimal-60-DBS were assessed for each patient. The numbers shown are absolute values of the mean ± SD or the median [IQR].
[c]Because the UPDRS-III total scores were normally distributed according to the Shapiro-Wilk *W* test, this analysis was by *t*-test.
[d]These are statistically significant *P* values.
[e]Secondary outcome measures were analyzed using the Mann-Whitney *U* test.
[f]Because 1 patient did not complete the Berg Balance Scale assessment, the analysis was based on data from 13 patients.
Abbreviations: Optimal-130-DBS, 130-Hz (high-frequency) deep brain stimulation at the optimal contact site; Optimal-60-DBS, 60-Hz (low-frequency) deep brain stimulation at the optimal contact site; SD, standard deviation; UPDRS, Unified Parkinson's Disease Rating Scale; IQR, interquartile range.

study protocol, including the method of active contacts optimization, see the Supporting Information and Supporting Figures 1 and 2.

The study was conducted with patients taking their usual antiparkinsonian medications. To minimize symptom fluctuation due to medication, each assessment session started at least 1.5 hours after administration of the usual levodopa dose and ended before the next dose (Supporting Fig. 2).[8,9] Each session lasted approximately 3 hours and was conducted in a single morning or afternoon to minimize circadian fluctuation. The off-medication state was not assessed for the patients' safety and comfort.

Study recruits were independent, ambulating patients with advanced PD who were treated with bilateral STN-DBS. For details of the inclusion criteria, see the Supporting Information. The Ethics Committee of Osaka University Hospital approved the protocol (approval no. 11256). All study patients provided written informed consent for their participation.

The primary outcome measure was the difference in total UPDRS-III score between the two stimulation conditions. Secondary outcome measures were UPDRS-III subscores, gait evaluated by means of the 10-meter timed walk test at preferred pace,[10] and postural stability evaluated by the Berg Balance Scale (BBS).[11] See Supporting Information for details of the outcome measures, assessments, and statistical analysis, according to the Consolidated Standards of Reporting Trials (CONSORT) guidelines.

Results

Sixteen patients were assessed for eligibility. One patient did not meet the inclusion criteria, and 1 patient who withdrew during the first stage 1 session was reluctant to participate in the 3-hour assessment. The remaining 14 patients were randomized and completed the study (Supporting Fig. 1). Patient characteristics and DBS settings are summarized in Supporting Tables 1 and 2, respectively.

Stage 1: Optimal Contacts for 60-Hz and 130-Hz Stimulations

Group analysis revealed a significant difference in the optimal contact positions between 60-Hz and 130-Hz stimulations ($P = 0.038$), with the optimal contacts for 60-Hz stimulation being more ventrally distributed (Supporting Fig. 3A,B). Individual analyses revealed that the optimal contact positions varied with respect to stimulation frequency in 5 of the 14 patients (Supporting Fig. 3C,D). Optimal contacts for 130-Hz and 60-Hz stimulations are shown for each patient in Supporting Table 3.

Stage 2: Immediate Effects of Optimal-60-DBS

Optimal-60-DBS yielded a mean UPDRS-III score of 4.6 points (standard deviation, 4.0 points) less than that of optimal-130-DBS ($P < 0.001$). No significant carry-over effect ($P = 0.603$) confounded the treatment effect (Table 1).

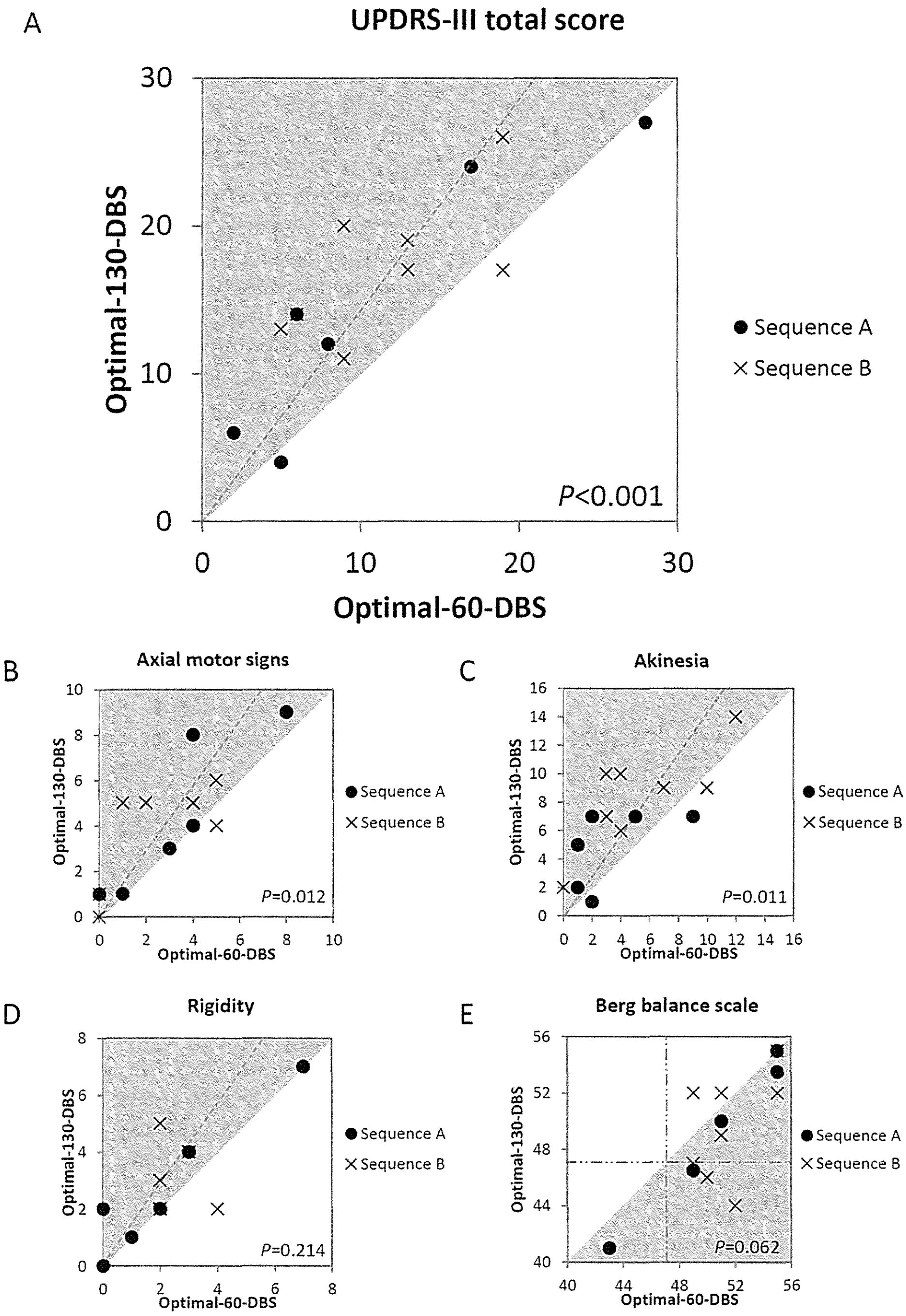

FIG. 1. (A-E) These scatter plots illustrate scores under 60-Hz and 130-Hz stimulation via the respective optimal contacts ("optimal-60-DBS" and "optimal-130-DBS", respectively). In **A** through **D**, the dashed lines correspond to the 30% score reductions produced by optimal-60-DBS. In **E**, the dashed-and-dotted lines correspond to the cutoff score of 47 for identifying patients who were at risk of falling.[12]

With respect to UPDRS-III subscores, optimal-60-DBS, compared with optimal-130-DBS, yielded significantly less severe axial motor signs ($P = 0.012$) and akinesia scores ($P = 0.011$). However, no significant difference between the 2 DBS conditions was observed in tremor ($P = 1.000$) or rigidity ($P = 0.214$) (Table 1). Optimal-60-DBS resulted in statistically significant less time ($P = 0.006$) and fewer steps ($P < 0.001$) needed to complete the 10-meter walk. No freezing of gait was observed under either DBS condition (Table 1), although most patients exhibited freezing of gait in the OFF-DBS condition. The BBS score tended to be higher under optimal-60-DBS ($P = 0.062$).

On an individual level, a good response (≥30% score reduction) to optimal-60-DBS was observed in 7 of the 14 patients in terms of total UPDRS-III score (Fig. 1A), in 5 patients in terms of axial motor signs (Fig. 1B), in 8 patients in terms of akinesia (Fig. 1C), but in only 3 patients in terms of rigidity (Fig. 1D). Slight tremor was observed in 5 patients, but the tremor subscores did not vary with the stimulation conditions (data not shown). Patients with PD who had a BBS score <47 reportedly are at risk of falling.[12] In our patient series, optimal-60-DBS, versus optimal-130-DBS, tended to result in fewer patients at risk of falling (Fig. 1E). Stimulation settings are shown for each patient in Supporting Table 3.

Adverse Effects

No serious or prolonged adverse effects attributed to the adjustment of stimulation settings were seen. Adjustment was frequently associated with transient paresthesia and mild dyskinesia in stage 1 (Supporting Table 4). No adverse effects were reported in stage 2.

Discussion

In this study, optimal-60-DBS had an immediate, positive effect on overall motor function in patients with PD. The 4.6-point improvement observed in this study is clinically important, because the minimal clinically important change in the UPDRS-III total score ranges from 2.3 to 5.0.[13,14] In terms of UPDRS-III subscores, optimal-60-DBS was better for controlling axial symptoms and akinesia and was equally as effective as optimal-130-DBS for controlling rigidity and tremor. On an individual level, optimal-60-DBS was more effective in improving total motor function in half of the patients and was comparable to optimal-130-DBS in the other half.

Optimal-60-DBS significantly reduced the time and number of steps required to complete the 10-meter walk. However, the importance of a 1-step/10-meter reduction and a 0.7-second/10-meter reduction is undetermined, because data substantiating the minimal clinically important change in these measures are lacking for PD patients.[15] Considering that most patients reported ease of walking during assessments under optimal-60-DBS (data not shown), we concluded that these relatively small differences are potentially substantial to improve gait in these patients. Although optimal-60-DBS was not superior for improving postural stability, it is potentially beneficial for reducing the risk of falling in patients with advanced PD.

Another important result is the difference in optimal contacts between 60-Hz and 130-Hz stimulations. The difference was observed in 36% of the patients, and the optimal contacts for 60-Hz stimulation were always relatively ventral whenever the difference in optimal contacts between frequencies was observed. This is interesting and worth further study, because the dorsolateral STN has long been recognized as the ideal target for DBS.[7] In fact, optimal-60-DBS similarly improved the UPDRS-III score in patients with more ventrally situated contacts and in patients with contact sites identical to the optimal-130-DBS contact sites. This was considered a result of the active contact optimization. Therefore, we believe that optimizing the active contacts with respect to frequency is very important in augmenting the beneficial effect of 60-Hz stimulation.

Because the study was not conducted under the off-medication condition and assessments were performed 1 hour after the change in stimulation, there was potential for a carry-over effect arising from the medication or first stimulation. However, the crossover design allowed for an analysis of any carry-over effect, which would manifest as a difference in the baseline measures within the time interval between the first and the second stimulations; no significant carry-over effect was found (Table 1). Thus, neither the timing of assessments relative to that of drug administration nor the short-term nature of the observations critically affected our results. Our study showed only the immediate effects of 60-Hz stimulation via the single monopolar contacts. It is very common for patients to have a transiently improved response to a change in stimulation. Despite the small sample size, which was another study limitation, optimal-60-DBS led to a significant improvement in the therapeutic effect of STN-DBS on motor symptoms. Overall, it will be important to test the long-term effects in controlled trials incorporating large numbers of patients and to test the effects using stimulation with more complex configurations, such as bipolar, tripolar, or multiple cathodes.

This study highlights the efficacy of relatively low-frequency stimulation via the optimal contacts in improving the overall motor function of patients with advanced PD who receive bilateral STN-DBS. This stimulation strategy improves axial symptoms without compromising the effect on segmental symptoms. Thus, the strategy is a potential option for patients who suffer axial symptoms despite successful STN-DBS. ■

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