MACULAR HOLES AND MACULAR PUCKER: THE ROLE OF VITREOSCHISIS AS IMAGED BY OPTICAL COHERENCE TOMOGRAPHY/SCANNING LASER OPHTHALMOSCOPY

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ABSTRACT

Purpose: The pathogenesis of macular pucker and macular holes is poorly understood. Anomalous posterior vitreous detachment (PVD) and vitreoschisis have been proposed as possible mechanisms. This study used clinical imaging to seek vitreoschisis and study the topographic features of macular pucker and macular holes.

Methods: Combined optical coherence tomography and scanning laser ophthalmoscopy (OCT/SLO) was performed in 45 eyes with macular hole and 44 eyes with macular pucker. Longitudinal imaging was used to identify vitreoschisis and measure retinal thickness. The topographic features of eyes with macular hole with eccentric macular contraction were compared to 24 eyes with unifocal macular pucker using coronal plane imaging.

Results: Vitreoschisis was detected in 24 of 45 eyes (53.3%) with macular hole and 19 of 44 (43.2%) with macular pucker. Retinal contraction was detected eccentrically in the macula of 18 of 45 eyes (40%) with macular hole. In eyes with macular hole with unifocal retinal contraction, the average surface area of contraction (23.12 ± 18.79 mm^2) was significantly smaller than in eyes with macular pucker (63.20 ± 23.68 mm^2; $P = .006$). The distance from the center of retinal contraction to the center of the macula was significantly greater in eyes with macular hole (8.64 ± 2.33 mm) than eyes with macular pucker (4.45 ± 1.90 mm; $P = .0001$).

Conclusion: Vitreoschisis was detected in about half of all eyes with macular hole and macular pucker. The topographic and structural features in eyes with macular hole with retinal contraction differed in comparison to eyes with macular pucker alone, suggesting that although each condition may begin with anomalous PVD, differences in subsequent cell migration and proliferation probably result in the different clinical appearances detected in this study.

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INTRODUCTION

The etiologies of macular hole and macular pucker are poorly understood. Disparate in symptoms as well as in ophthalmoscopic features and imaging, these two conditions have long been considered distinctly different entities. Past theories of the pathogenesis of macular holes included ocular trauma,[1] cystic degeneration,[2] and ocular angiospasm.[3] In recent years, emergent theories proposed that vitreous plays an important role in the formation of macular holes.[4,5] Similarly, theories on the development of macular pucker have evolved over time. One theory is that microbreaks in the retina caused by posterior vitreous detachment (PVD) allow for the migration of fibroblasts, glial cells, and astrocytes from the retina to the surface of the internal limiting lamina, where they proliferate.[6]

The most recent hypothesis is the unifying concept of anomalous PVD,[5] which proposes that the first event in the pathophysiology of both macular hole and macular pucker is the same. Collapse of the liquefied vitreous body without sufficient dehiscence at the vitreoretinal interface can induce a split within the posterior vitreous cortex (vitreoschisis), leaving the outermost layer of the posterior vitreous cortex attached to the macula. To date, attempts to elucidate pathogenesis have been hampered by a lack of adequate imaging technology.

Combined optical coherence tomography/scanning laser ophthalmoscopy (OCT/SLO) was used to study eyes with macular holes and macular pucker in search of vitreoschisis. Quantitative analysis of the topographic features of these 2 conditions was undertaken using the unique features of this imaging technology.

METHODS

SUBJECTS

Eighty-nine (89) eyes from 85 consecutive patients evaluated between March 2005 and November 2006 at the VMR Institute in Huntington Beach, California (n = 56) and the New York Eye and Ear Infirmary (n = 33) were selected on the basis of having either a macular hole (n = 45) or macular pucker (n = 44). This study was in conformity with all federal and state laws, and all HIPAA guidelines have been followed. Institutional review board approval for the retrospective analysis of these data has been obtained.

OCT/SLO IMAGING

Fundus imaging was performed using combined OCT/SLO imaging (Ophthalmic Technologies Inc, Toronto, Canada), which consists of a dual-channel system incorporating an interferometer and a confocal receiver. A broadband infrared superluminescent diode with a wavelength of 820 nm provides the light source used by the OCT/SLO. In the longitudinal mode, the OCT/SLO projects light through

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a Galvano scanning mirror system, moving the beam in a horizontal line to create cross-sectional images of the retina. In the coronal (created by transverse scanning) imaging mode, the light is projected through 2 X,Y Galvano scanners moving the beam in a raster fashion across the surface of the retina. Each coronal plane image that is produced is an X,Y image at a different Z-axis depth. The depth resolution is approximately 10 µm, and the transverse resolution is approximately 20 µm. For both the coronal and longitudinal OCT scans, a matching grayscale confocal fundus image is produced and displayed alongside.

In coronal plane imaging, the grayscale SLO confocal fundus image (Figure 1A) and the threshold color OCT image in the coronal plane (Figure 1C) can be superimposed. There is point-to-point correspondence between the 2 images (coronal OCT and SLO; Figure 1B), since they are obtained simultaneously using parallel detector systems. The superimposed images were especially useful for identifying centers of retinal contraction in each subject. A pucker contraction center was defined as an area where radially oriented retinal striations converged. The center of an area of retinal contraction was determined using 3-dimensional rendering (manufacturer-provided) of the intersection between a longitudinal OCT scan and the SLO image (Figure 2). The point on the longitudinal OCT scan that corresponded to the macular pucker contraction center, as visualized by convergent striations, was defined as the center of retinal contraction. This point was used to measure retinal thickness from the internal limiting lamina of the retina to the anterior aspect of the outer layer of the double laminar structure representing the choriocapillaris/retinal pigment epithelium interface,[7] using the calibrated calipers of the OCT/SLO software (Figure 3).

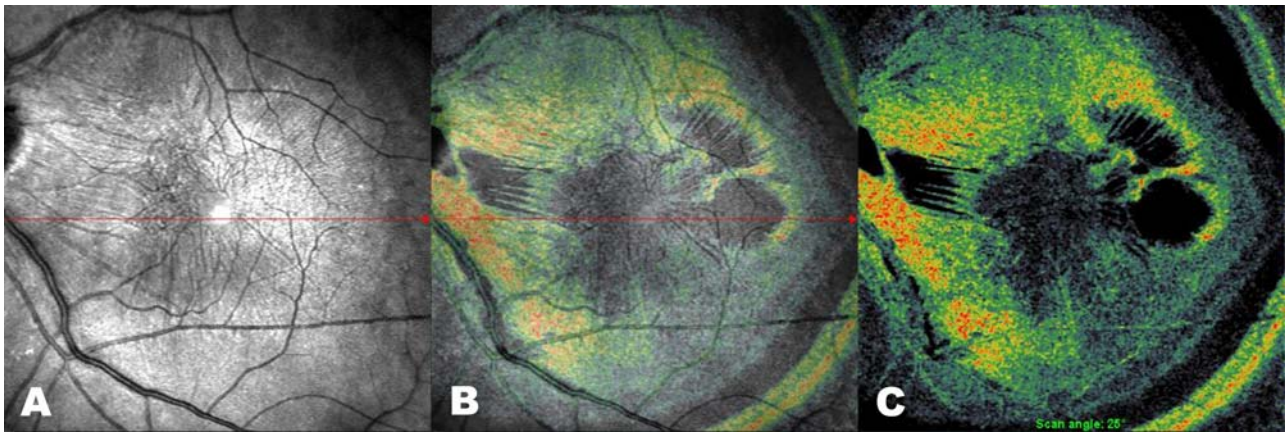


FIGURE 1

Analysis of topographic features in macular pucker. A, Grayscale SLO image of the fundus in a subject's left eye. B, Overlay of the coronal OCT image (color photo C) superimposed on the SLO fundus image (grayscale photo A) with point-to-point registration. C, Coronal plane OCT image, in color. The overlay image (B) was used to characterize the macular hole and/or macular pucker (as in this case) for topographic analysis.

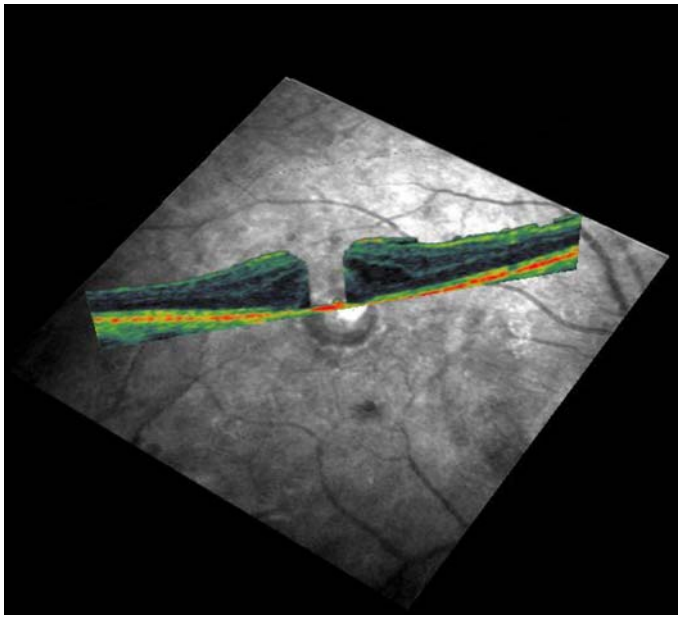


FIGURE 2

Intersecting planes analysis of macular hole. Three-dimensional reconstruction of a transverse OCT image at 45 degrees intersecting with the SLO fundus image of a patient with a macular hole. The point that was identified as the center of contraction on the fundus/SLO overlay corresponded to the same point on OCT, which was used to perform retinal thickness measurement.

The SLO fundus images with superimposed coronal plane OCT scans were analyzed quantitatively with Adobe PhotoShop software (Figure 4). The diameter of the contraction center was determined by visualizing the region of the pucker where the striations

converged in confluence. The ruler function of the software was used to measure the diameter. This value was then divided in half to yield the radius, which was used to calculate the surface area of pucker. The ruler was also used to measure the distance between the retinal contraction centers and the center of the macula.

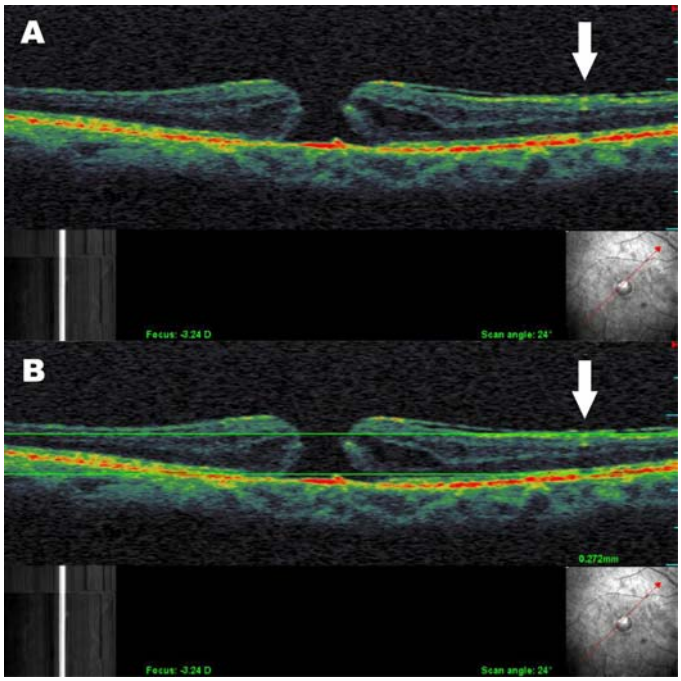


FIGURE 3

Quantitative analysis of retinal contraction in macular hole. Longitudinal OCT imaging was performed at an axis of 45 degrees (red line with arrowhead on the small grayscale SLO images of fundus; to the right). A, White arrow points to the center of eccentric retinal contraction identified by 3-dimensional rendering. B, White arrow demonstrates the vertical caliper function used to measure retinal thickness (272 μm at that point).

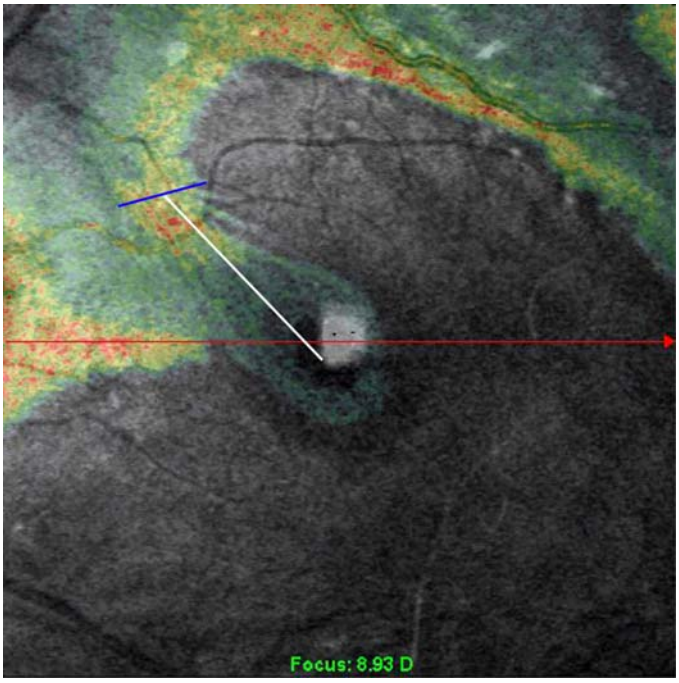


FIGURE 4

Quantitative analysis of coronal plane OCT images in macular holes. Measurement of the distance from the center of contraction to the center of the macular hole and the diameter of retinal contraction area was performed using Adobe Photoshop software. The white line is a representation of the ruler function used to measure the distance between the macular hole and the center of the macular pucker. The blue line is a representation of the ruler function used to measure the diameter of the contraction center for calculation of contraction area.

STATISTICAL ANALYSIS

The 2-sample *t* test assuming equal variance was used to evaluate the statistical significance of differences found in this study.

RESULTS

MACULAR HOLE

There were 18 men and 27 women, with a mean age of 64.7 ± 14.4 years. In 18 eyes (40%) with macular hole, there were areas of retinal contraction identified in the peripheral macula (Figure 5). Table 1 shows the clinical characteristics of this group. Five eyes (27.8%) had stage 2 macular hole, 10 (66.7%) had stage 3 macular hole, and 3 (16.7%) had stage 4 macular hole. A single focus of retinal contraction was identified in 13 of 18 eyes (72%), and 2 centers of retinal contraction were identified in 4 of 18 eyes (22.2%). Only 1 eye with macular hole had more than 2 centers of retinal contraction.

MACULAR PUCKER

There were 27 men and 17 women with a mean age of 62 ± 12.2 years. Clinically, all eyes with macular pucker had definite pucker, with distinct corrugation of the underlying retina on longitudinal OCT. Of the 44 eyes with macular pucker, 20 eyes (45.5%) had multiple retinal contraction centers. Two centers were found in 11 (25.0%), 3 centers in 5 (11.4%), and 4 centers in 4 (9.1%). Twenty-four eyes (54.5%) had unifocal macular pucker (Table 2). PVD was detected by B-scan ultrasonography in 18 of 24 eyes (75%).

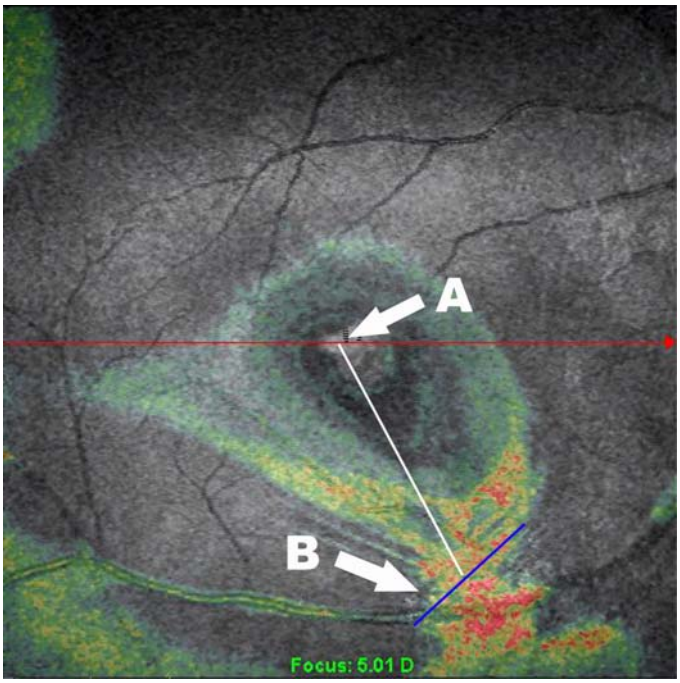


FIGURE 5

Retinal contraction in macular holes. Coronal plane image (color) superimposed on grayscale SLO fundus image of a macular hole (A) with an eccentric focus of macular pucker (B).

TABLE 1. CLINICAL CHARACTERISTICS OF 18 EYES WITH MACULAR HOLE (MH) AND UNIFOCAL RETINAL CONTRACTION

AGE/SEX	VA	MH STAGE	VITREOSCHISIS*	MH DIAMETER	AREA OF CONTRACTION, mm^2	DISTANCE FROM CENTER OF MH TO CENTER OF CONTRACTION, mm
60M	20/60	2	+	310	16.55	8.69
65M	20/80	2	-	320	…	…
69F	20/400	4	+	800	…	…
64F	20/200	3	+	400	26.6	5.24
76F	20/400	3	+	280	…	…
72F	20/400	3	-	900	12.95	11.37
56M	72/400	3	-	460	…	…
54M	HM	3	-	390	…	…
100F	CF	3	-	510	…	…
81F	20/100	2	+	210	10.64	11.21
66F	20/150	3	-	650	8.66	6.03
62F	…	4	+	640	21.32	10.57
53M	20/80	2	-	210	29.22	9.22
61M	20/400	3	-	790	73.14	5.41
67F	CF	3	+	490	18.4	10.03
79F	20/400	2	-	240	…	…
67F	CF	3	-	580	13.72	8.59
86M	CF	4	-	750	…	…

CF, counting fingers; HM, hand motions; VA, visual acuity.
*Plus sign indicates present, minus sign indicates absent.

TABLE 2. CLINICAL CHARACTERISTICS OF 24 EYES WITH UNIFOCAL MACULAR PUCKER

AGE/SEX	VA	VITREOSCHISIS	PVD	RETINAL THICKNESS AT CONTRACTION CENTER, µm	AREA OF RETINAL CONTRACTION, mm^2	DISTANCE FROM CENTER OF MACULA TO THE CENTER OF ECCENTRIC RETINAL CONTRACTION, mm
68M	20/30	+	+	355	114.8	2.28
59M	20/20	-	-	175	4.08	7.6
59M	20/20	-	+	241	37.18	5.19
58F	20/25	+	-	465	66.19	2.32
63M	20/20	-	+	439	76.05	3.37
63M	20/30	+	+	395	110.67	1.57
65F	20/26	-	+	175	7.21	7.15
46F	20/30	+	+	395	47.91	1.75
59M	20/20	-	+	421	91.44	3.01
67F	20/30	-	+	281	12.32	5.81
66F	20/30	+	-	491	173.9	1.35
68M	20/26	-	+	404	57.55	3.01
69F	20/30	-	+	443	97.12	2.04
74F	20/26	-	+	202	28.65	7.46
71M	20/60	-	+	539	28.84	5.01
74M	20/26	-	-	360	13.72	11.57
74M	20/40	+	-	351	58.09	8.13
63M	20/30	-	-	342	26.06	2.68
69M	20/25	-	+	263	72.38	4.04
75F	20/26	+	+	399	79.17	6.46
48F	20/20	-	+	289	161.73	2.29
60F	20/20	-	+	219	25.61	8.28
60F	20/40	+	+	342	84.95	2.03
66M	20/26	+	+	373	41.28	2.37

PVD, posterior vitreous detachment; VA, visual acuity.
*Plus sign indicates present, minus sign absent.

VITREOSCHISIS

Vitreoschisis was considered present when 2 membranous layers were seen to join into one, forming the shape of "lambda" or the letter *Y*. With this definition, longitudinal OCT imaging detected vitreoschisis in 24 of 45 eyes (53.3%) with macular hole (Figure 6) and 19 of 44 eyes (43.2%) with macular pucker (Figure 7).

TOPOGRAPHIC ANALYSIS OF MACULAR HOLE VS MACULAR PUCKER

Eyes with macular hole and only one center of retinal contraction (n = 13) were compared to eyes with macular pucker and similarly only one center of retinal contraction (n = 24). Of the eyes with macular hole, 3 had poor coronal plane images, making quantitative analysis of topography unreliable. Thus, the 10 eyes with macular hole and unifocal retinal contraction that also had usable coronal plane images were compared with the 24 eyes with unifocal macular pucker with respect to the surface area of retinal contraction, distance of the contraction center from the center of the macula, and the degree of underlying retinal thickening. The results are presented in Table 3.

Surface Area

The average retinal contraction surface area in eyes with macular hole was 23.12 mm^2 ± 8.79 mm^2. The average pucker surface area in eyes with macular pucker was 63.20 mm^2 ± 23.68 mm^2. The difference in retinal contraction surface areas between eyes with macular hole and eyes with macular pucker (analyzed by Student's *t* test assuming equal variance) was statistically significant (*P* = .006).

Distance From Fovea

In eyes with macular hole, the average distance from the center of retinal contraction to the center of the macular hole was 8.64 mm ± 2.33 mm. In eyes with macular pucker, the average distance from the center of retinal contraction to the foveola was 4.45 mm ± 1.90

mm. The difference in distances from the center of retinal contraction to the center of the macula in macular hole vs macular pucker eyes was statistically significant ($P = .0001$), as analyzed by Student's *t* test assuming equal variance.

Retinal Thickness

In eyes with macular hole, the average retinal thickness at the center of retinal contraction was 295 μm ± 130 μm. The average retinal thickness at the center of contraction in eyes with macular pucker was 0.348 μm ± 0.117 μm. The difference between these groups was not statistically significant ($P = .1$).

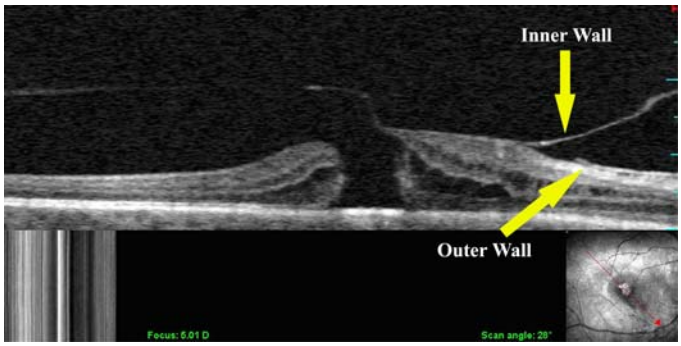


FIGURE 6

Vitreoschisis in macular hole. Longitudinal OCT and SLO imaging of the vitreoretinal interface in an eye with a stage 3 macular hole demonstrates the two walls (inner wall is anterior, toward the top of the photo; outer wall is posterior, toward the bottom of the photo, attached to the inner surface of the retina) of vitreoschisis.

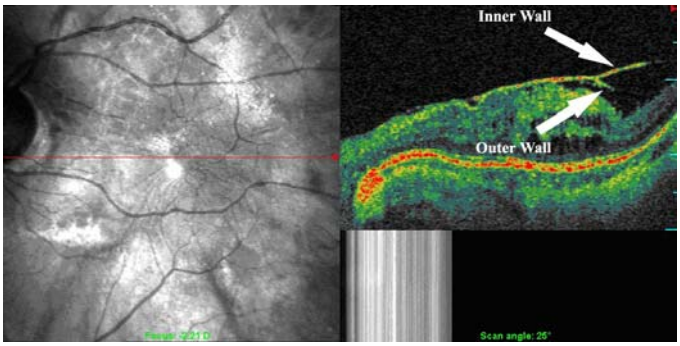


FIGURE 7

Vitreoschisis in macular pucker. Longitudinal OCT and SLO (right) imaging of the vitreoretinal interface demonstrates the two walls (inner wall is anterior, toward the top of the photo; outer wall is posterior, toward the bottom of the photo) of vitreoschisis forming a "lambda" sign where they rejoin.

TABLE 3. TOPOGRAPHIC FEATURES OF 24 EYES WITH UNIFOCAL MACULAR PUCKER (MP) COMPARED TO 10 EYES WITH MACULAR HOLE (MH) AND ECCENTRIC UNIFOCAL RETINAL CONTRACTION

FEATURE	MP EYES (n = 24)	MH EYES (n = 10)	*P* VALUE
Retinal contraction surface area (mm^2)	63.20 ± 23.68	23.12 ± 8.79	.006
Distance to center of macula (mm)	4.45 ± 1.90	8.64 ± 2.33	.0001
Retinal thickness (μm)	348 ± 117	295 ± 130	.1

DISCUSSION

Investigations into the pathogenesis of macular holes and macular pucker have been hampered by the lack of experimental models and adequate imaging technologies. Using combined OCT/SLO imaging, heretofore unidentified features of the vitreoretinal interface in macular hole and macular pucker could be analyzed both qualitatively and quantitatively. Vitreoschisis was found in half of all eyes. This is likely related to the underlying multilamellar structure of the posterior vitreous cortex (Figure 8), which can split into separate layers during anomalous PVD. Previously detected in proliferative diabetic retinopathy,[8-10] vitreoschisis has not been described in macular hole and macular pucker and was probably found in this study owing to the increased resolution of the combined OCT/SLO technology. The "lambda" (Y-shaped) configuration seen in Figures 6 and 7 demonstrates that 2 layers arise from a split in the lamellar posterior vitreous cortex. Although the remaining cases in this study did not feature the "lambda" sign, there were many eyes that had a visible posterior vitreous cortex anterior to the retina with a distinct membrane attached to the anterior surface of the retina. Although this was not considered vitreoschisis in this study, future studies with higher-resolution imaging might be able to ascertain whether the incidence of vitreoschisis is even greater than identified in this investigation.

These studies found that 40% of eyes with macular hole had evidence of an eccentric premacular membrane with retinal contraction. However, there were more cases with multiple foci of retinal contraction in eyes with macular pucker (45.5%) than in eyes with macular hole (28%). What's more, retinal contraction centers in eyes with macular hole were 3 times smaller (23 vs 63 mm^2; $P = .006$) than the retinal contraction centers in eyes with macular pucker. Thus, if anomalous PVD were indeed an important

event in macular hole and macular pucker, there must be some other factors to account for the dissimilar clinical and topographic features of the two conditions.

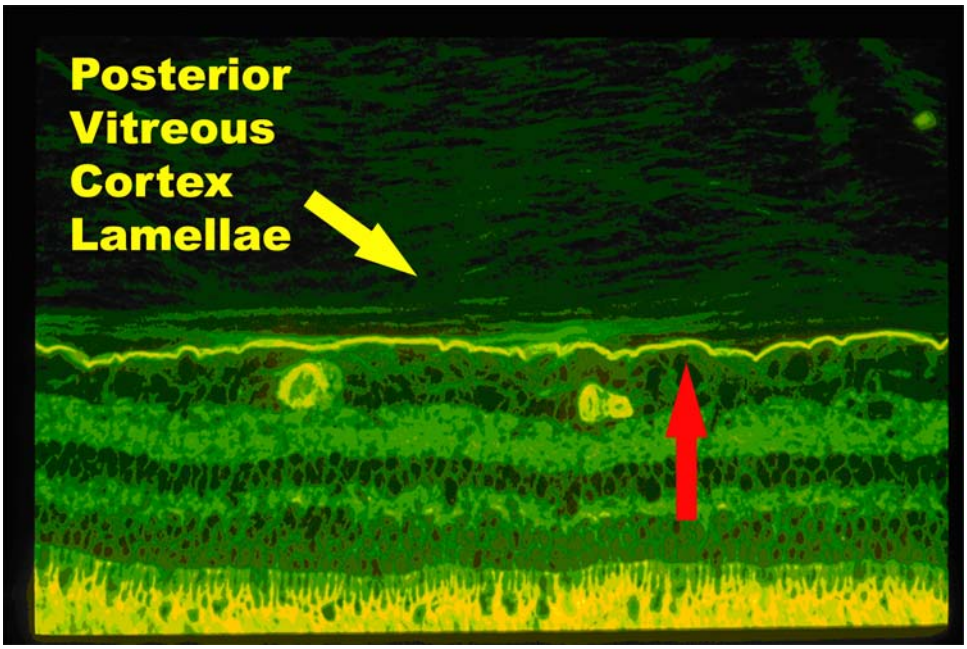


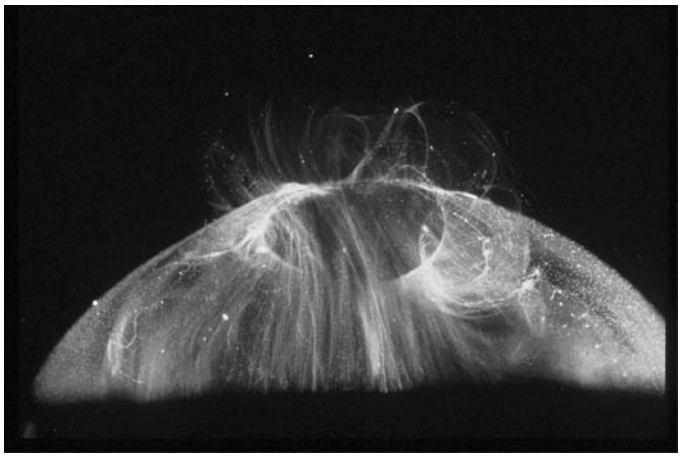
FIGURE 8

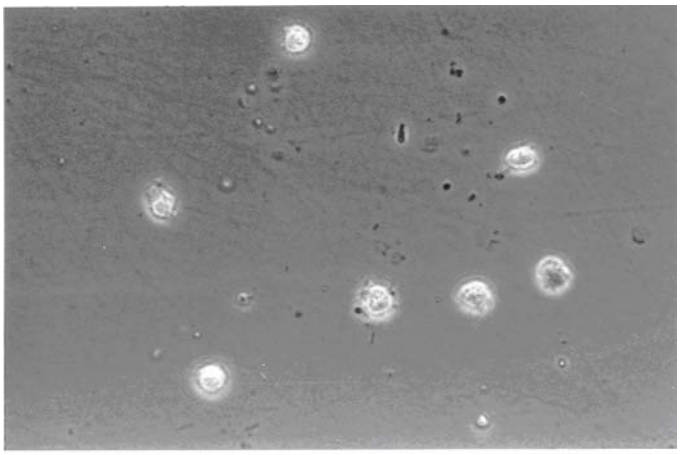
Lamellar structure of posterior vitreous cortex. Immufluorescent micrograph of human vitreoretinal interface. Using anti-ABA lectin binding, the internal limiting lamina stains intensely as a horizontal line in the middle of this photograph, and the lamellae of the posterior vitreous cortex are apparent anterior to this line. (Courtesy of Dr Greg Hageman, University of Iowa)

One difference between macular hole and macular pucker could be the level at which vitreoschisis splitting occurs during anomalous PVD.[4] As shown in Figure 8, there are many lamellae within the posterior vitreous cortex. Also present within the posterior vitreous cortex are hyalocytes (Figure 9). These mononuclear phagocytes are embedded within the posterior vitreous cortex,[11-13] approximately 50 μm from the internal limiting lamina of the retina.[14,15] If the level of the vitreoschisis split in the posterior vitreous cortex occurs posterior to the level of hyalocytes, these cells will detach away from the retinal surface along with the anterior portion of the vitreous cortex. This is likely what happens in macular hole, leaving a relatively hypocellular layer of vitreous attached to the macula. The relative paucity of cells left on the surface of the retina could account for the findings reported herein: that a minority (40%) of eyes with macular hole have retinal contraction; that in those eyes with macular hole with retinal contraction, the number of contraction centers is never more than 2 (compared to 3 and 4 centers in macular pucker); and the surface area of these retinal contraction centers is relatively small. At surgery, these membranes are relatively thin and more difficult to engage than are the membranes found in macular pucker.

In eyes with macular pucker, the vitreoschisis split likely occurs more anteriorly, leaving hyalocytes attached to the macula. As mononuclear phagocytes of the reticuloendothelial cell system, *sentinel* hyalocytes can stimulate the migration and proliferation of monocytes from the systemic circulation and glial cells from the retina, resulting in more pucker centers and larger areas of retinal contraction, as was found in the present study. Indeed, studies[16] have shown that hyalocytes may play an important role in proliferative disorders of the retina via the release of connective tissue growth factor. Other studies[17] have furthermore shown that hyalocytes can induce collagen gel contraction in response to platelet-derived growth factor and other cytokines. Thus, hyalocytes are likely important in stimulating cell proliferation as well as inducing tangential vitreoretinal contraction, the two main components of macular pucker.

In conclusion, the findings of this study support the hypothesis that vitreoschisis occurs in macular holes and macular pucker, probably as a result of anomalous PVD. Future studies should be undertaken to correlate histopathologic analysis of tissue removed at surgery with clinical and OCT/SLO topography, so as to determine whether the cellular compositions are consistent with the differences noted on clinical evaluation and imaging. This should test the hypothesis that vitreoschisis in macular holes splits posterior to the level of hyalocytes, whereas splitting of the posterior vitreous cortex in macular pucker occurs anterior to the level of hylaocytes. Indeed, while vitreomacular pathophysiology may be more complex than previously thought, and while we wish to understand it as basically as possible, we should attempt to follow Albert Einstein's sage advice: "Make everything as simple as possible, but not simpler."





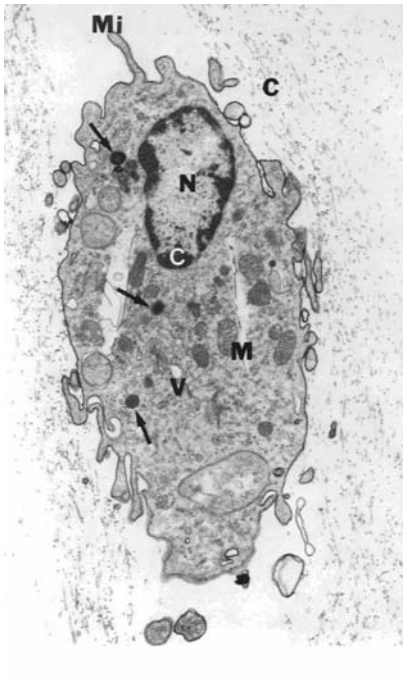


FIGURE 9

Top left, Human hyalocytes in situ. Dark-field slit microscopy of the posterior vitreous in a 59-year-old man. Arrow indicates hyalocytes embedded within the posterior vitreous cortex. Top right, Explanted human posterior vitreous cortex with hyalocytes. Phase contrast microscopy of hyalocytes in the posterior vitreous cortex of an 11-year-old girl. The specimen was fresh and unfixed (original magnification, ×290). (Specimen courtesy of New England Eye Bank). Bottom, Ultrastructure of human hyalocyte. Transmission electron micrcograph of human hyalocyte embedded in the dense collagen matrix of the posterior vitreous cortex (black C) (original magnification, ×11,670). Mi, microvilli, typical of phagocytes; N, lobulated nucleus with dense marginal chromatin (white C); M, mitochondria; V, vacuole; black arrows indicate cytoplasmic dense granules. (Courtesy of Joe Craft and Dr Daniel Albert, Cogan Laboratory of Ophthalmic Pathology, Harvard Medical School)

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REFERENCES

1. Noyes HD. Detachment of the retina, with laceration at the macula lutea. *Trans Am Ophthalmol Soc* 1871;1:128.
2. Coats G. The pathology of macular holes. *Roy Lond Hosp Ophthalmic Rep* 1907;17:69.
3. Gifford SR. An evaluation of ocular angiospasm. *Trans Am Ophthalmol Soc* 1943;48:19.
4. Gass JD. Idiopathic senile macular hole. Its early stages and pathogenesis. *Arch Ophthalmol* 1988;106:629-639.
5. Sebag J. Anomalous posterior vitreous detachment: a unifying concept in vitreo-retinal disease. *Graefes Arch Clin Exp Ophthalmol* 2004;242:690-698.
6. Foos RY. Nonvascular proliferative extraretinal retinopathies. *Am J Ophthalmol* 1978;86:723-725.
7. Pons ME, Garcia-Valenzuela E. Redefining the limit of the outer retina in optical coherence tomography scans. *Ophthalmology* 2005;112:1079-1085.

8. Kakehashi A, Schepens CL, de Sousa-Neto A, Jalkh A, Trempe CL. Biomicroscopic findings of posterior vitreoschisis. *Ophthalmic Surg* 1993;24:846-850.
9. Chu TG, Lopez PF, Cano MR, et al. Posterior vitreoschisis. An echographic finding in proliferative diabetic retinopathy. *Ophthalmology* 1996;103:315-322.
10. Schwartz SD, Alexander R, Hiscott P, Gregor Z: Recognition of vitreoschisis in proliferative diabetic retinopathy. A useful landmark in vitrectomy for diabetic traction retinal detachment. *Ophthalmology* 1996;103:323-328.
11. Bloom GD, Balazs EA. An electron microscopic study of hyalocytes. *Exp Eye Res* 1965;4:249.
12. Sebag J. *The Vitreous—Structure, Function, and Pathobiology*. New York: Springer-Verlag; 1989:43-51.
13. Lazarus HS, Hageman GS. In situ characterization of the human hyalocytes. *Arch Ophthalmol* 1994;112:1356-1362.
14. Sebag J. Surgical anatomy of vitreous and the vitreo-retinal interface. In: Tasman W, Jaeger EA, eds: *Clinical Ophthalmology.* Vol 6. Philadelphia: JB Lippincott; 1994: chap 51.
15. Qiao H, Hisatomi T, Sonoda KH, et al, The characterisation of hyalocytes: the origin, phenotype, and turnover. *Br J Ophthalmol* 2005;89:513-517.
16. Kita T, Hata Y, Kano K, et al. Transforming growth factor-beta2 and connective tissue growth factor in proliferative vitreoretinal diseases: possible involvement of hyalocytes and therapeutic potential of Rho kinase inhibitor. *Diabetes* 2007;56:231-238.
17. Hirayama K, Hata Y, Noda Y, et al: The involvement of the rho-kinase pathway and its regulation in cytokine-induced collagen gel contraction by hyalocytes. *Invest Ophthalmol Vis Sci* 2004;45:3896-3903.

PEER DISCUSSION

DR C. P. WILKINSON: This interesting paper describes the use of a new imaging modality, combined optical coherence tomography and scanning laser ophthalmoscopy (OCT/SLO). Together, these provide simultaneous pixel-to-pixel images from both devices, and this technique should be of significant value in improving our understanding of a variety of vitreoretinal disorders.

So-called anomalous posterior vitreous detachment (PVD)[1] is a concept that has been postulated by Dr Sebag for several years and includes (1) vitreous liquefaction with an accumulation of fluids in the premacular portion of the vitreous cavity; (2) varying degrees of persistent adhesion between the posterior cortical vitreous and the internal limiting membrane (ILM); (3) splitting, or "vitreoschisis," of the posterior cortical vitreous at the time of PVD; and (4) residual islands of cortical vitreous attached to the ILM following separation of the majority of the gel from the surface of the retina. He has described this entity as important in the pathogenesis of a variety of important disorders, including macular holes (MH), idiopathic epiretinal membrane (ERM) formation, vitreomacular traction syndrome, proliferative diabetic retinopathy, diabetic macular edema, retinal tears, and additional problems.

In this report the authors compared ERMs in eyes with MH to those with idiopathic ERM alone, termed macular pucker (MP) cases. ERMs were present in 40% of eyes with MH. Compared to idiopathic MP cases, ERMs in MH eyes were smaller and their centers were located farther from the fovea. Similar retinal thicknesses were discovered beneath the centers of the ERMs in both groups of cases. Only 2 (11%) of the 18 MH cases had a complete PVD, whereas this was observed in 18 (75%) of the24 MP eyes. Visual acuities were substantially better in the MP cases.

Apparent vitreoschisis was identified in 24 (53%) of 45 eyes with MH and 19 (43%) of 44 MP cases. The authors propose (1) that vitreoschisis at varying levels within the posterior vitreous cortex may be responsible for the differences in ERMs associated with these entities, and (2) that the ERMs are derived from hyalocytes or that these cells stimulate ERM formation by other types of cells.

The burning question posed by a reading of this manuscript is the viability of the authors' proposition of anomalous PVD as the best explanation for these macular disorders. It is now generally accepted that some degree of PVD plays an important role in the pathogenesis of both MH and ERM formation and that islands of residual vitreous cortex frequently remain on the inner surface of the retina following both spontaneous and surgically created PVD. Still, the debate regarding the types of cells that produce ERMs and the means by which they reach the retinal surface has continued for decades, and this study does not provide information that assists in solving the puzzle.

Ultrastructural and immunocytochemical analyses are more likely than imaging studies to improve our understanding regarding ERM formation. Published data that are at odds with the authors' opinions include (1) a study by Messmer and associates[2] that demonstrated similar electron microscopic features of ERMs associated with both MP and MH cases; (2) a report by Chen and coworkers[3] demonstrating a lack of correlation between residual islands of retained vitreous cortex at surgery and postoperative ERM formation; and (3) a publication by Snead and colleagues[4] that implicated glial cells as responsible for ERMs associated with both MP and MH. Still, I suppose it may be possible that metaplastic hyalocytes theoretically could assume characteristics of glial cells.

The authors' conclusions appear to me to invoke a more complicated explanation or theory than is necessary, and this might appear to be a violation of "Ockham's razor" that "entities should not be multiplied unnecessarily," ie, the simplest viable explanation may be most likely to be the best. A simpler explanation has long been offered, and this is that PVD typically begins posteriorly near the foveloa and then extends more peripherally. The speed with which this occurs has recently been brought into question in Mark Johnson's excellent 2005 AOS thesis, and transient or persistent foveolar and macular adhesions to the cortical vitreous may be responsible for a variety of maculopathies. Regardless, following even small amounts of PVD, cells can gain access to the retinal surface through a MH or through breaks in the ILM caused by PVD. I believe this rather old theory continues to provide a rational explanation of ERM formation, although it could be incorrect. My primary question for the authors, what are the weaknesses in the premise that this older explanation may be the best?

The authors are to be congratulated and thanked for introducing us to this exciting new imaging technique and for stimulating us

with interesting material. My negative comments are intended as "constructive criticism," and one should bear "Hanlon's razor" in mind: "Never attribute to malice that which can be adequately explained by stupidity."

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REFERENCES

1. Sebag J. Anomalous posterior vitreous detachment: a unifying concept in vitreoretinal disease. *Graefes Arch Clin Exp Ophthalmol* 2004;242:690-698.
2. Messmer EM, Heidenkummer H, Kampic A. Ultrastructure of epiretinal membranes associated with macular holes. *Graefes Arch Clin Exp Ophthalmol* 1998;236:248-254.
3. Chen TY, Yang CM, Liu KR. Intravitreal triamcinalone staining observation of residual undetached cortical vitreous after posterior vitreous detachment. *Eye* 2006;20:423-427.
4. Snead DRJ, Cullen S, James S, et al. Hyperconvolution of the inner limiting membrane in vitreomaculopathies. *Graefes Arch Clin Exp Ophthalmol* 1998;236:248-254.

DR. LEE. JAMPOL: No conflict. Do you feel that with this imaging technology you can distinguish clearly between epiretinal tissue, the posterior hyaloid with glial cell proliferation, the walls of the vitreoschisis cavity, and other membranes? In other words, is it easy to tell these apart or is it difficult? This information may help in determining which of these various theories might be correct.

DR. JOHN T. THOMPSON: No conflict. Did you find a difference in the age of the macular hole among the eyes with epiretinal membranes compared to those that were not associated epiretinal membranes? What I am really trying to determine is, do you think that the epiretinal membrane is a secondary event in older macular hole eyes where cells have entered the vitreous somehow? Do you believe that this may be part of the pathogenesis of macular hole formation and may explain why internal limiting membrane peeling and removal of the epiretinal membrane may improve the success of the surgery?

DR. TIM STOUT: No conflicts. There seems to be a question regarding the origin of these cells. If the hyalocytes are present in these membranes, what is known about the integrins that are expressed on their cell surface? I ask because integrins are key components in cell to cell communications. A whole new collection of compounds, the cyclopeptides, are known to very specifically inhibit certain integrins. It strikes me that if we knew more about the integrins expressed by hyalocytes, then we could develop very useful therapy.

DR. ALLAN J. FLACH: I have no conflicts. I would like to thank the presenter for a beautifully edited presentation. You put great effort in presenting a large volume of information into a tiny amount of time. I would like to learn the opinion of retinal specialists present regarding what we should call this condition. Would it be better for us to call "posterior vitreous detachment" simply "posterior vitreous separation", so that our patients do not tell their comprehensive ophthalmologists they have a "retinal detachment"?

DR. JERRY SEBAG: I would like to thank Pat Wilkinson for his discussion and excellent contribution to this presentation. I thank Dr. Flach for his compliments, but the presentation is far better than it would have been as a result of the constructive criticism of Pat. This study poses two questions: what are the weaknesses of the old theories and are the findings better explained by anomalies of vitreoretinal traction and vitreoschisis? The old theories hypothesize that cells migrate through a break in the internal lamina in the case of macular pucker, and through a hole in the macula, in the case of macular holes; however, this finding has never been observed histologically. Observing a cell in a certain location is a very different matter than implicating its pathogenic action. A dynamic situation that involves migration and vitreoschisis, on the other hand, has been demonstrated with echography, histopathologic studies, and now with optical coherence tomography (OCT). The old theories do not explain the stimuli that underlie the migration or proliferation. Hyalocytes are sentinel macrophages that recruit the migration of cells primarily from circulation, but in this instance also aberrantly derived cells from the retina. Connective tissue growth factor is known to be released by hyalocytes. The old theories do not explain the contractile forces on these membranes. Hyalocytes produce components of the rho kinase pathway that are known to powerfully stimulate membrane contraction. The old theories do not explain why macular pucker tissue is hypercellular and why the tissue surrounding macular holes is hypocellular in composition. Anomalous posterior vitreous detachment (PVD) hypothesizes that if vitreoschisis occurs anterior to the hyalocytes then the residual membrane is hypercellular. This membrane becomes even more hypercellular if these cells elicit migration of monocytes from the circulation and glial cells from the retina. Vitreoschisis that occurs posterior to the hyalocytes results in membranes that are hypocellular and macular hole formation. Observation during surgery suggests that macular pucker membranes extend to the peripheral fundus. This finding is more consistent with the anatomy of the posterior vitreous cortex. Anomalous PVD with vitreoschisis results in a large sheet, as opposed to the islands of residual tissue that were suggested by Kishi. In macular hole surgery, the existence of the second membrane posterior to the vitreoschisis explains an increase in macular hole closure rate from 76% to 100% with its removal. As you will hear tomorrow from John Thompson, and it is our experience, if we are aggressive about dissecting farther posteriorly, then we observe a higher closure rate with macular hole surgery. The theory of anomalous PVD with vitreoschisis supports that observation. Lastly, in spite of my strong desire to agree with

our esteemed colleague and friend, Pat Wilkinson, and to accept the premise that the simplest viable explanation is most likely the best, I quote Albert Einstein and heed his sage advice. He recommends "make everything as simple as possible, but not simpler".

Concerning the questions of Dr. Jampol, he wanted to know if it was possible to distinguish between epiretinal tissue, posterior vitreous cortex, and other membranes with this technology. I believe that the resolution of this current technology is just at the border of making that differentiation, Very shortly, in fact in two weeks, I will be receiving the spectral domain OCT. It is my expectation, based on observations I have made with the time domain version, that the higher resolution spectral domain will provide a more precise and reliable method to distinguish between these various tissues. John Thompson questions whether the difference in the age of the macular hole may have relevance in terms of the formation of these membranes. He asks if they are a secondary event or part of the primary pathophysiology. It is my opinion that these membranes are an essential part of the pathophysiology. There can be further thickening with older membranes and the spectral domain instrument will likely provide more exact measurements. We will be able to measure these and, with a sufficiently large data base, also be able to perform statistical analysis and to correlate the thickness of these membranes with the age of the macular hole. I believe that these membranes exist at the very beginning of the pathophysiologic process in this condition. Tim Stout questions whether integrins are present on the surface of hyalocytes. I believe resident macrophages are usually in a quiescent stage and function as sentinels that undergo up-regulation in response to certain noxious situations. I believe that future studies should be done to identify the up-regulation of integrins. This process is extremely important, not only in explaining the movement of these cells, but in understanding the stimulation, migration, and proliferation of the other cells that were previously mentioned.

Lastly, I do speak to patients in terms of "posterior vitreous separation" because I have had the same problem. Your point is well taken and our literature should reflect our clinical experience.