The introduction of the ophthalmoscope by Hermann von Helmholtz in 1851, and later modifications to produce the binocular indirect ophthalmoscope by Charles Schepens in 1945, allowed visualization of the retina, optic nerve, and vitreous cavity. These developments were turning points in ophthalmology because they allowed physicians to visualize structures that were previously imperceptible.

The anatomy of the vitreous is vitally important in normal and diseased states, such as vitreomacular traction, macular holes, and diabetic tractional retinal detachments. Yet the vitreous anatomy typically remains obscured because it is largely transparent to visible light.

In this installment of Practical Retina, Gerardo Ledesma-Gil, MD; Pedro Fernández-Avellaneda, MD; Talia R. Kaden, MD; and Michael Engelbert MD, PhD, all from New York City, discuss visualization of the human vitreous in vivo. Optical coherence tomography, particularly swept-source, has been one of the major imaging advances to drape the proverbial sheet over the ghost. Their original research and comprehensive overview of recent advances in understanding the vitreous anatomy are sure to enlighten the retina community.

By volume, the vitreous is the largest component of the eye and yet it is often overlooked by both comprehensive ophthalmologists and retina specialists alike. In part, this is because it is difficult to see, both on clinical exam and on multimodal imaging. However, the latter is beginning to change, and in the process, much is being learned about this enigmatic structure.

The vitreous gel is a virtually acellular, highly hydrated (> 98% water) extracellular matrix. Its structure is maintained by a network of unbranched collagen fibrils comprised of collagen types II, V, IX, and XI. The glycosaminoglycan (GAG) hyaluronan is a major component that fills the spaces between these collagen fibrils. Although essential to the optical properties of the eye, the fact that it is an almost optically clear medium composed mainly of water makes it difficult to accurately describe its anatomical state.

Initially, the only source of information available was through in vivo biomicroscopic observations with an ophthalmoscope or a slit-lamp, providing a good but somewhat superficial insight as to its structure. Ex vivo histologic studies were unreliable due to numerous post-fixation artifacts caused by the high water content of the samples. This changed in 1976 when Jan Worst injected ink into the vitreous of postmortem eyes and identified a system of liquid spaces within the vitreous gel consisting of what he called the premacular bursa and cisterns surrounding the latter. Georg Eisner continued to expand our understanding when he used a modified slit-lamp camera to analyze postmortem eyes and not only confirmed Worst’s findings, but also discovered areas of lower optical density in the vitreous cortex above the vessels, which he named “lücken,” (“gaps”), or prevascular fissures. In 1990, Kishi and Shimizu stained the vitreous with fluorescein in cadaveric eye specimens. They discovered that the premacular bursa was separated from the retina posteriorly by a thin layer of cortical tissue. They also defined the bursa as a boat-shaped, confined space.

doi: 10.3928/23258160-20200603-01
that developed connections with other spaces only after a degenerative process of the vitreous.\textsuperscript{8} To emphasize this, they changed the term premacular bursa to posterior precortical vitreous pocket (PPVP). With the development of vitrectomy and use of intraocular stains, these structures were later visualized using triamcinolone intraoperatively.\textsuperscript{9}

**THE VITREOUS IN THE OCT ERA**

With the advent of optical coherence tomography (OCT), our understanding of in vivo ocular anatomy, and pertinently, vitreous anatomy, has expanded dramatically. Many have utilized the enhanced imaging capabilities of OCT to better understand the vitreous.\textsuperscript{10,11} In 2014, we developed an imaging protocol that allowed us to enlarge the size of the area scanned to $18 \times 18$ mm using swept-source OCT (SS-OCT).\textsuperscript{12} This approach made it possible to demonstrate that the premacular bursa is limited inferiorly, but contrary to what had been previously reported, continues superiorly beyond the reach of our instruments (Figures 1C and 1D).\textsuperscript{13} This scan-
This separation disappears superiorly at a variable distance from the optic nerve, thereby creating a connection between these two spaces (Figure 1B). This differs from the small connection proposed by Kishi et al., who used SS-OCT to describe a connection between the PPVP and Cloquet’s canal. It also differs from the supposed connection between the premacular bursa and the retrociliary circle of cisterns proposed by Worst. Instead, we pictured these spaces like a mitten, with the thumb part over the area of Martegiani, the finger and palm part over the macula, and the wrist and arm making their way towards the front of the eye, possibly terminating behind the lens in the space of Erggelet (Figure 1). The overall shape of the premacular bursa appears to be uniform early in life but may vary in size, as seen in a father and son with Stickler’s disease. They presented with a “giant premacular bursa,” which may represent an optically empty vitreous in the setting of attached cortical vitreous.

Our recent work also supported some of Eisner’s work on prevascular fissures. In our study of normal volunteers, we detected thin hyporeflective spaces in the vitreous overlying first- and second-order blood vessels in young individuals without...
vitreous degeneration, corroborating the presence of the spaces Eisner had first described decades ago (Figure 2). With time, the vitreous is known to degenerate and these fissures appear to transform into bigger spaces, which likely correspond to the cisterns Worst described (Figure 3). Fissure planes in the more central vitreous appear also related to this degenerative process. A recently described aspect is the lamellar arrangement of fibers in the vitreous cortex. A novel model of fibrillar vitreous architecture characterized by a pattern of eyewall-parallel vitreous fibers with a tangential course toward the equator forms the vitreous cortex with some perpendicular fibers delimiting spaces deep inside the vitreous (premacular bursa, prepapillary gap, and prevascular fissures and cisterns). This lamellar pattern is compatible with the idea that with time and as degenerative changes ensue, the lamellae begin to separate, potentially resulting in vitreoschisis.

**CLINICAL AND SURGICAL CORRELATIONS**

Knowledge of the normal vitreous anatomy and its characteristic aging changes is helpful in the clinical and surgical setting. For instance, it is well known that abnormal hyaloid adherence and tangential traction are implicated in the pathogenesis of vitreomacular traction (VMT) and macular hole (MH) formation. However, the status of the vitreous may also play an important role in those disorders. Although it might seem intuitive that eyes with advanced vitreous degeneration would have higher rates of macular holes or VMT, in fact, the opposite may be true. In a comparative study of eyes with VMT and MH versus control eyes, the former demonstrated significantly earlier stages of vitreous degeneration as compared to their matched controls, even when the latter were on average, younger. This may be because a degenerated vitreous creates a compartmentalization that buffers the inertia counterforces to the vitreoretinal interface (Figure 4), whereas a well-formed structure more effectively transmits any force applied to it. Going forward, this may allow for better prognostication for our patients regarding the likelihood of developing a vitreoretinal interface disease. It may also facilitate treatment, or one might postulate that a treatment that advances vitreous degeneration may concurrently reduce the risk of VMT or MH.
A better in vivo understanding of the vitreous can also be helpful in the postoperative course, as was true in this report in which SS-OCT was used to identify residual cortical vitreous in a patient with persistent floaters after surgery that were otherwise invisible on clinical examination (Figure 5).29

The vitreous also plays an outsized role in the development of other intraocular diseases, including and especially in diabetes mellitus. Although known to impact the metabolic regulation throughout the body, in the vitreous, diabetic changes can lead to early liquefaction and cross-linking of the collagen network in a process known as diabetic vitreous degeneration.20

Figure 4. Eyes on the vitreomacular traction (VMT)-macular hole (MH) spectrum were found to be more likely to have a relatively intact vitreous gel (A), whereas eyes with an uneventful contralateral posterior vitreous detachment and no VMT in the study eye were significantly more likely to show more extensive vitreous degeneration with fissure planes (P = .048) (B, C). Diagrammatic horizontal section of an eye with formed vitreous, with saccadic forces being transmitted from more central formed vitreous onto the vitreoretinal interface without mitigation (D), whereas compartmentalization in an eye with more advanced vitreous degeneration and fissure planes buffers these forces (E). Adapted from: Ghadiali Q, Zahid S, Dolz-Marcos R, Tan A, Engelbert M. An Assessment of Vitreous Degeneration in Eyes with Vitreomacular Traction and Macular Holes. J Ophthalmol. 2017:2017:6834692.

Figure 5. Widefield image (left) of a 28-year-old myope who complained of a crescentic opacity in his superotemporal peripheral field after undergoing vitrectomy for symptomatic vitreous opacities. Swept-source optical coherence tomography (1 and 2) demonstrated that a posterior vitreous detachment had been induced (red arrowhead), but that there was a residual posterior hyaloidal skirt with scalloped edges, presumably from cutter bites (green arrowhead). Further propagation of the vitreous separation and close shaving of the gel relieved this patient of his symptoms. Adapted from: Chen KC, Jung JJ, Engelbert M. Swept source optical coherence tomography of the posterior vitreous after pars plana vitrectomy. Graefes Arch Clin Exp Ophthalmol. 2015;253(11):2041-2043.
In a 2017 paper exploring the relationship between retinal neovascularization in patients with diabetic retinopathy and the posterior vitreous, nearly 80% of these membranes had grown along the outer surface of the posterior hyaloid face. Even the classic “wolf’s jaw” configuration of neovascularization, which has been shown to track along the venous arcades, proliferates along the posterior hyaloid. However, in the setting of a largely attached vitreous cortex, the neovascularization can penetrate the posterior hyaloid and grow along the walls of prevascular fissures or cisterns, giving rise to flat, broad and tightly adherent plaques that can be challenging to tackle surgically. Given this information, a clear understanding of the relationship between diabetic neovascularization and the vitreous can not only aid in understanding this disease but also in surgical planning for these patients (Figure 6). Finally, the idea suggested by Kishi that the boat-shaped preretinal hemorrhages are confined to the...
premacular bursa and that their morphology is accounted for by the shape of the latter, was dismissed. OCT showed that the premacular bursal wall is permeable to erythrocyte passage, and an intrabursal bleed is followed by rapid infiltration of the adjacent vitreous gel by erythrocytes, giving rise to a hemorrhage with more indistinct margins (Figure 7).

**CONCLUSION**

The vitreous is a complex structure that involved in diverse pathologic processes. As our multi-modal imaging capabilities have expanded, so too has our understanding of in vivo anatomy and with that, the opportunity to better understand vitreoretinal pathology. Further research will continue to grow this knowledge base and provide an even more complete understanding of the vitreous and its impact.

**REFERENCES**


---

**Figure 7.** Intrabursal hemorrhage due to Valsalva retinopathy. Ophthalmoscopy revealed a boat-shaped hemorrhage with indistinct margins adjacent to the inferior vascular arcade and a second hemorrhage inferior to the optic disk (A). There was no leakage identified on fluorescein angiography, but blockage over the vein the hemorrhage likely originated from B (red arrowhead). The vitreous was imaged using swept source optical coherence tomography, and the areas imaged with line scans are illustrated in the reflectance image (C). Note that erythrocytes are predominantly localized within the vitreous gel between the premacular bursa (stars) and the cortical vitreous. The bursal cavity itself is relatively devoid of erythrocytes; however, accumulation of erythrocytes within the vitreous adjacent to the bursa creates the impression that the bursal wall is lined with blood. Also note that the vitreous is attached at the macula, and the subhyaloid space is optically clear without any evidence of hemorrhage. Adapted from: Balaratnasingam C, Vaz-Pereira S, Engelbert M. Intrabursal and Subhyaloid Hemorrhages in Valsalva Retinopathy. *Retina.* 2017;37(1):e1-e3.
Gerardo Ledesma-Gil, MD, can be reached at Vitreous Retina Macula Consultants of New York, 950 3rd Ave, 3rd floor, New York, NY 10022; email: gerardo.ledesmagil@gmail.com.

Pedro Fernández-Avellaneda, MD, can be reached at Vitreous Retina Macula Consultants of New York, 950 3rd Ave, 3rd floor, New York, NY 10022; email: pedro.dezavellaneda@gmail.com.

Talia R. Kaden, MD, can be reached at Department of Ophthalmology, Manhattan Eye, Ear and Throat Hospital, New York, New York; email: talia.kaden@gmail.com.

Howard F. Fine, MD, MHSc, can be reached at can be reached at Rutgers Robert Wood Johnson Medical School; New Jersey Retina, 10 Plum Street, Suite 600, New Brunswick, NJ 08901; email: hfine@njretina.com.

Michael Engelbert MD, PhD, can be reached at Vitreous Retina Macula Consultants of New York, 950 3rd Ave., 3rd floor, New York, NY 10022; email: michael.engelbert@gmail.com.

Disclosures: Dr. Engelbert is a consultant for Genentech, Bayer, Allergan, and Alimera Sciences. Dr. Fine is a consultant and/or speaker for Alimera, Allergan, Genentech, Regeneron, and Spark Therapeutics and has equity/patent interests in Auris Surgical Robotics. The remaining authors report no relevant financial disclosures.