Diplomarbeit

Etiology and timing of vitrectomy in eyes with non-diabetic vitreous hemorrhage

eingereicht von

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unter der Anleitung von

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Graz, 25.02.2019

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Graz, am 25.02.2019 *Markus Eidherr eh*

DANKSAGUNGEN

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ZUSAMMENFASSUNG

ZIELSETZUNG: Es wurden die Ursachen von Glaskörperblutungen, welche zu einer erstmaligen Vitrektomie in den Augen von nicht-diabetischen Patienten und Patientinnen führten, sowie der Zeitpunkt der Operation und die Entwicklung der Sehleistung, untersucht.

STUDIEN DESIGN: Retrospektive vergleichende Fallserie.

METHODEN: Alle Augen von nicht-diabetischen Patienten und Patientinnen, in welchen eine erstmalige Vitrektomie mit der Hauptdiagnose “Glaskörperblutung” im Zeitraum von 2000 bis 2015 durchgeführt wurde, wurden untersucht. Ausschlusskriterien waren eine vorherige Vitrektomie am betroffenen Auge, sowie die Diagnose Diabetes Mellitus. Zielgrößen waren die Ätiologie der Glaskörperblutung, der Zeitpunkt des chirurgischen Eingriffs, sowie die Entwicklung der Sehleistung. Abhängig vom Zeitraum zwischen Erstvorstellung und Vitrektomie wurden die Patienten und Patientinnen in eine frühzeitige Vitrektomie Gruppe (≤30 Tage) und eine abwartende Vitrektomie Gruppe (>30 Tage) geteilt. In weiterer Folge wurden die Unterschiede in den Ursachen und der Sehleistungsentwicklung zwischen den beiden Gruppen ermittelt.

ERGEBNISSE: 161 Augen von 158 Patienten und Patientinnen wurden in die Studie aufgenommen. Mit 27,3% waren retinale Venenverschlüsse am häufigsten ursächlich für eine Glaskörperblutung. Netzhautrisse mit Netzhautablösung verursachten in dieser Studie häufiger Glaskörperblutungen als Netzhautrisse ohne Netzhautablösung (11,8% bzw. 7,5%). Eine Glaskörperabhebung ohne Netzhautriss wurde in 8,7% der Augen als Ursache der Glaskörperblutung ermittelt. Die Vitrektomie erfolgte im Durchschnitt 65,1 ± 65,7 Tage nach der Erstvorstellung. In 46,2% der in dieser Studie eingeschlossenen Augen wurde der Eingriff innerhalb der ersten 30 Tage nach Erstvorstellung durchgeführt. Frühzeitig operiert wurde signifikant häufiger in Augen, in welchen eine Netzhautablösung, ein Trauma oder eine Operationskomplikation ursächlich für die Glaskörperblutung waren. Die durchschnittliche Zeit bis zur Operation betrug in der frühzeitigen Vitrektomie Gruppe 12,8 ± 9,2 Tage, verglichen mit 93,3 ± 70,6 Tage in der abwartenden Vitrektomie Gruppe. Eine chirurgische Intervention verbesserte die Sehleistung sowohl in Augen welche frühzeitig operiert wurden als

auch in Augen in welchen zuerst abgewartet wurde, signifikant. Im Endvisus konnte kein Unterschied zwischen den beiden Gruppen festgestellt werden.

SCHLUSSFOLGERUNG: Zahlreiche Krankheiten können einer nicht-diabetischen Glaskörperblutung, welche eine Vitrektomie erfordert, zugrunde liegen. Die häufigsten sind retinale Venenverschlüsse, hintere Glaskörperabhebungen und Netzhautrisse mit oder ohne Netzhautablösung. Unabhängig vom Zeitpunkt des Eingriffes, verbessert eine Vitrektomie die Sehleistung signifikant.

ABSTRACT

OBJECTIVE: The causes of vitreous hemorrhage, including the timing of surgical intervention and the development of visual acuity in eyes of non-diabetic patients who underwent first-time vitrectomy were studied.

STUDY DESIGN: Retrospective comparative case series.

METHODS: All eyes of non-diabetic patients that underwent first-time vitrectomy with the main diagnosis “vitreous hemorrhage” in the period from 2000 to 2015 were evaluated. Exclusion criteria were a previous vitrectomy on the affected eye or the diagnosis of diabetes mellitus. Main outcome measures were the etiology of vitreous hemorrhage, the timing of surgical intervention and the development of visual acuity. Depending on the time interval between initial presentation and vitrectomy patients were split into an early vitrectomy group (<30 days) and a delayed vitrectomy group (>30 days). Subsequently, differences in the etiology and the visual development between both groups were analyzed.

RESULTS: 161 eyes of 158 patients were included in this study. Most common cause for vitreous hemorrhage was retinal vein occlusion with 27.3%. Retinal tears with retinal detachments more often caused vitreous hemorrhage in our study than retinal tears without retinal detachment (11.8% and 7.5%, respectively). Vitreous detachment without retinal tear was causative for vitreous hemorrhage in 8.7%. Mean time between initial presentation and vitrectomy was 65.1 ± 65.7 days. Early vitrectomy was performed in 46.2% of the eyes and significantly more often in eyes with retinal detachment, trauma or an operative complication underlying vitreous hemorrhage. Mean time to surgery in this group was 12.8 ± 9.2 days, compared to 93.3 ± 70.6 days in the delayed vitrectomy group. Vitrectomy improved vision significantly in both groups and no difference in the final visual acuity was found between the two of them.

CONCLUSION: Various diseases can cause vitrectomy-requiring vitreous hemorrhage in non-diabetic patients. Retinal vein occlusion, posterior vitreous detachment and retinal tears with or without retinal detachment were identified as the most common indications for vitrectomy. Vitrectomy improves vision significantly, independent of when surgery is performed.

INHALTSVERZEICHNIS

GLOSSAR UND ABKÜRZUNGEN

ACA	ANTERIOR CILIARY ARTERIES
AMD	AGE-RELATED MACULAR DEGENERATION
BCVA	BEST CORRECTED VISUAL ACUITY
BRAO	BRANCH RETINAL ARTERY OCCLUSION
BRVO	BRANCH RETINAL VEIN OCCLUSION
C3F8	OCTAFLUOROPROPANE
CRAO	CENTRAL RETINAL ARTERY OCCLUSION
CRVO	CENTRAL RETINAL VEIN OCCLUSION
CS	CENTISTOKES
HA	HYALURONIC ACID
HRVO	HEMIRETINAL VEIN OCCLUSION
ILM	INNER LIMITING MEMBRANE
IOP	INTRAOCULAR PRESSURE
IVI	INTRAVITREAL DRUG INJECTION
logMAR	LOGARITHM OF THE MININMAL ANGLE OF RESOLUTION
OA	OPHTHALMIC ARTERY
PCA	POSTERIOR CILIARY ARTERIES
PDR	PROLIFERATIVE DIABETIC RETINOPATHY
PVD	POSTERIOR VITREOUS DETACHMENT
PVR	PROLIFERATIVE VITREORETINOPATHY
RD	RETINAL DETACHMENT
RPE	RETINAL PIGMENT EPITHELIUM
RRD	RHEGMATOGENOUS RETINAL DETACHMENT
RVO	RETINAL VEIN OCCLUSION
SD	STANDARD DEVIATION

SF6	SULFUR HEXAFLUORIDE
US	ULTRASOUND
WFNS	WORLD FEDERATION OF NEUROSURGICAL SOCIETIES

ABBILDUNGSVERZEICHNIS

TABELLENVERZEICHNIS

1 INTRODUCTION

1.1 THE RETINA

The Retina develops from a diverticulum of the forebrain (prosencephalon) by what it can be described functionally and evolutionarily as a protruded part of the brain. It forms the innermost layer of the eyeball and consists of three cascaded neurons: photoreceptors, bipolar cells and ganglion cells.[1,2]

Incident light passes various retinal layers until it reaches the photoreceptors. Two types of photoreceptors exist: rods and cones. Cones are responsible for vision under daylight conditions, whereas rods are essential for mesopic and scotopic vision. The center of the macula lutea is the avascular fovea centralis. It contains exclusively cones and is responsible for sharp vision. The peripheral retina contains both types of photoreceptors and is important for general orientation.[1–3]

Bipolar cells receive the signals from the photoreceptors and transmit them to the retina's innermost neuron, the ganglion cells. The 1.1 million ganglion cell axons unite at the papilla where they form the optic nerve, which transmits the received and processed light stimulus to the visual center of the brain.[2]

Special glia cells, referred to as Müller's supporting cells, span all retinal layers and fill in most of the intercellular space.[4] They maintain the mechanical cohesion of the different retinal layers and play an important role in the ion distribution during the retina's process of excitation.[2,4]

Following the path of incident light, nine individual layers of the retina and two anatomical structures below can be described:[1–3]

- Inner limiting membrane (ILM): Basement membrane of Müller's supporting cells. Separating the retina from the vitreous body.
- Nerve fiber layer: Ganglion cell axons.
- Ganglion cell layer: Ganglion cell nuclei.
- Inner plexiform layer: Synapses between the axons of the bipolar cells and the dendrites of the ganglion cells.

- Inner nuclear layer: Nuclei of the bipolar cells and interneurons. Interneurons (horizontal cells and amacrine cells) provide a horizontal processing of information.
- Outer plexiform layer: Synapses between the axons of the photoreceptor cells and the dendrites of the bipolar cells.
- Outer nuclear layer: Nuclei of the photoreceptor cells.
- Outer limiting membrane: Connection of Müller's supporting cells among each other and with the photoreceptor cells.
- Outer segments of photoreceptors.
- Retinal pigment epithelium (RPE): Single cubic layer formed by heavily pigmented epithelial cells lying underneath the neurosensory retina. RPE cells are important for the function of the photoreceptor cells.
- Bruch's membrane: Basement membrane of the choroid. Separating the retina from the choriocapillaris.

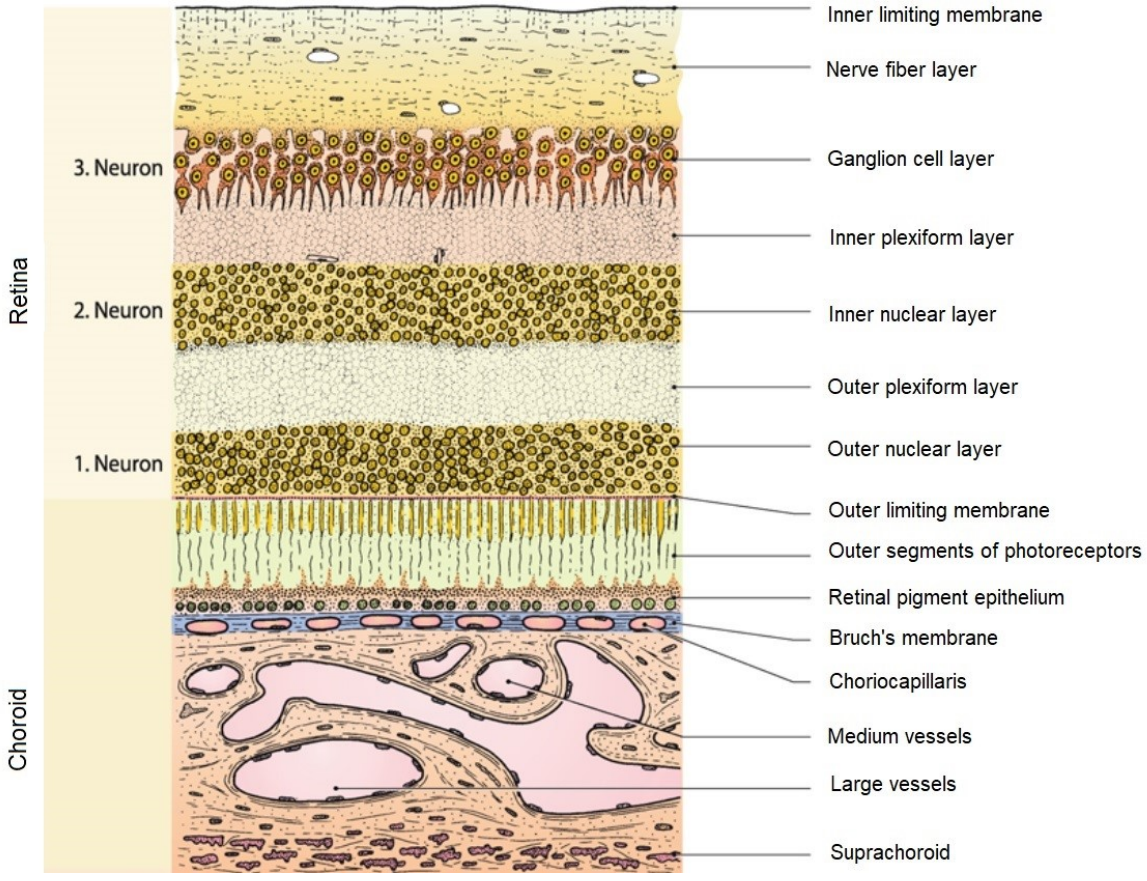

Figure 1: Schematic cross-section of the retina and the choroid.[2] Used with the kind permission of Springer.

1.2 THE EYE'S BLOOD SUPPLY

The delivery of oxygen and other nutritive substrates to the retina is accomplished by two separate vascular systems, the retinal and uveal system. Vessels of both systems derive from the ophthalmic artery (OA), a branch of the internal carotid artery.[5]

1.2.1 The retinal system

The OA gives off the central retinal artery which enters the optic nerve 6-15mm behind the globe from where it maintains its position up to the optic disc. At the level of the optic disc it is further divided into four branches, each supplying one quadrant of the retina.[4,5]

The larger retinal vessels lie close to the ILM within the innermost part of the retina and maintain a close relationship with glia cells. Terminal arterioles branch off the retinal arteries at almost 90°. A plexus of capillaries emerges from the arterioles and forms a two-layer network that supplies the inner two thirds of the retina. The superficial retinal capillary plexus lies in the nerve fiber and ganglion cell layer, the deep retinal capillary plexus subsides in the inner nuclear layer and disappears towards the periphery. An additional capillary network lies in the superficial portion of the nerve fiber layer in the peripapillary area. This network generates the radial peripapillary capillaries that are found around the optic disc and the temporal superior and inferior retinal vessels. Capillary-free zones are close to the arterioles and the fovea.[5]

The terminal vessels of the retinal system, the precapillary arterioles and the postcapillary venules, are linked in the capillary bed. The venous system has a similar structure as the arterial system. It drains the blood out of the capillaries towards the central retinal vein that leaves the eye through the optic nerve and leads the blood to the cavernous sinus.[5]

1.2.2 The uveal system

The choroid, which is composed of the choriocapillaris layer, Sattler's layer (medium vessels layer) and Haller's layer (outer layer of larger vessels), is supplied by the ciliary arteries. The posterior ciliary arteries (PCA) and the recurrent anterior ciliary arteries (ACA) both arise from the OA and supply the corresponding hemispheres of the choroid and the deeper third of the retina. Ten to twenty short PCAs enter the globe at the posterior pole, split into small choroid branches and form the Zinn/Haller Plexus of vessels around the optic nerve. Two long PCAs, one nasally and one temporally, draw to the anterior segment of the eye where they form vascular networks with the ACA. The ACA arise from the extraocular muscle arterial branching of the OA and form the episcleral circle and the innermuscular circle before they proceed to the major circulus arteriosus of the iris where they unite with the two long PCA. ACA primarily supply the ciliary body and the iris. Additionally, the ACA are divided into recurrent branches that supply the anterior choroid.[4,5]

In the peripapillary area and the submacular area the choriocapillaris appears as a dense network of freely connected capillaries. At the posterior pole the choriocapillaris is organized in a lobule-like arrangement of 0.6-1mm, consisting of a radially and circumferentially arranged capillary meshwork with a central arteriole and a venule in its periphery. Blood is discharged from the lobules by collecting venules that join the afferent veins. The subcapillaris plexus is formed by vessels of larger lumen that drain the blood into 4-6 vortex veins that flow into the superior and inferior orbital veins. Additional drainage is provided by the anterior ciliary veins of the ciliary body.[4,5]

1.3 THE VITREOUS BODY

The vitreous body is a transparent, avascular gel that is filling in the space between the lens, the ciliary body and the retina. It has a volume of approximately 4ml and is making up around 65% of the human eyeball. The vitreous consists of 98-99% water. The remaining 1-2% are composed by collagen and hyaluronic acid (HA).[1,4,6]

In its function the vitreous is a stabilizer and shock absorber for movement or mechanical irritations.[1,4,6] By having the same refractive index as the aqueous fluid (1.33) it is also a refractive medium. Furthermore it provides a conduit for the metabolic requirements of the lens as well as a barrier to inhibit migration of cells and macromolecules from the retina to the vitreous cavity.[2,7]

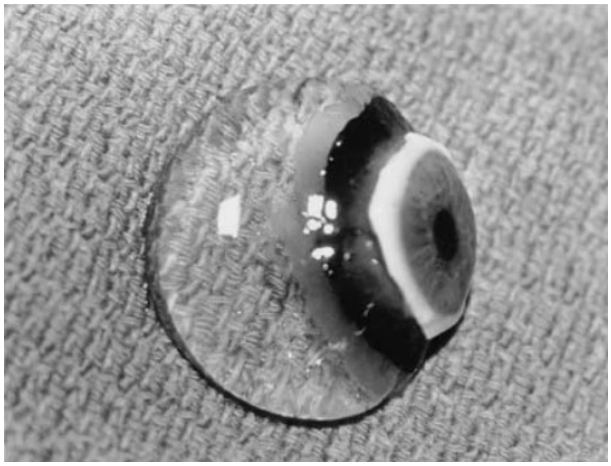

Figure 2: Vitreous of a 6-month-old child still attached to the anterior segment.[8] Used with the kind permission of Springer Nature

The most anterior part of the vitreous is a thin collagenous layer called anterior hyaloid. Directly posterior is the semi-transparent vitreous base which is firmly attached to the ciliary body and the retina. The anterior border of the vitreous base is located at the pars plana of the ciliary body. The posterior border extends 2-3mm posteriorly of the ora serrata which is the dividing area between the retina and the ciliary body. The vitreous base is less viscous than the vitreous core that comprises the entire central region of the vitreous body and is covered by a very thin collagenous layer called vitreous cortex or hyaloid membrane.[9]

The vitreous cortex is formed by condensed peripheral collagen fibrils.[1]

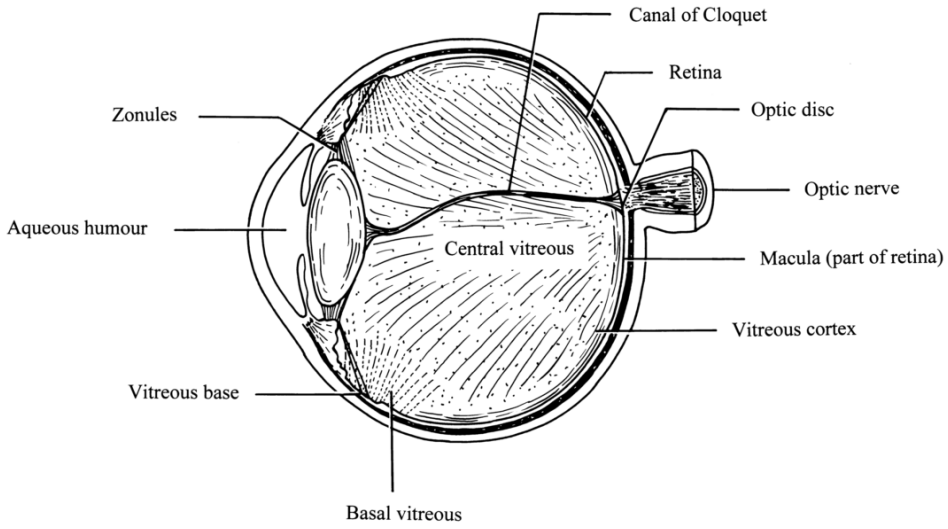

Figure 3: Anatomy of the vitreous and surrounding structures.[7] Used with the kind permission of Elsevier.

The ultrastructure of the vitreous is a highly specified extracellular matrix consisting mainly of macromolecules, HA and collagen.[10] Packed bundles of collagen fibrils are forming linear fibers that are oriented in an antero-posterior direction inserting anteriorly in the vitreous base and posteriorly in the vitreous cortex overlying the macula. Large HA molecules and water molecules are filling the space between the collagenous fibers and are entangled with a loose network of non-oriented collagen fibrils.[11] The vitrosin, as the vitreous body collagen is called, originates mainly from the neural retina, the vitreous itself and the hyalocytes.[12]

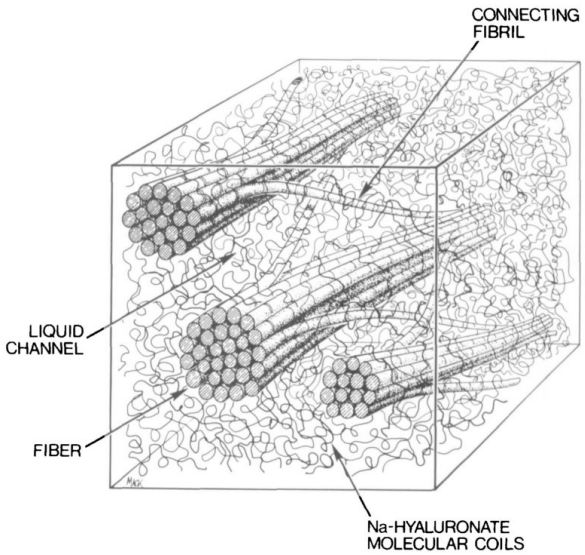

Figure 4: Schematic ultrastructure of the vitreous.[11] Used with the kind permission of the Association for Research in Vision and Ophthalmology

Hyalocytes are cells of the vitreous body. They are located in the vitreous base and the vitreous cortex and are organized in a monolayer surrounded by collagen fibers.[13] In a study on rodent eyes Qiao et al[14] showed that hyalocytes are positive for ED2 confirming their identification as tissue macrophages. Furthermore, they found out that hyalocytes derive from bone marrow and are replaced within 7 months of time.

Thus the effect of hyalocytes on the vitreous cavity environment can be subdivided into 3 categories: production of vitreous extracellular matrix, modulation of immune reaction and modulation of inflammation.[15]

Furthermore antioxidants such as ascorbic acid, cysteine, uric acid, tyrosine and glutathione are found in a significant concentration in mammalian vitreous.[16] These antioxidants play an important role in protecting ocular tissues from radiation, oxygen radicals and exposure to hydrogen peroxide and other oxidants.[17]

Chen-Roetling et al[18] found out that the vitreous' antioxidants may also play an important role in the relative resistance of retinal neurons to hemorrhagic injury by protecting the neurons from hemoglobin toxicity.

1.3.1 Vitreoretinal Interface

The vitreoretinal interface is the area of contact between the vitreous and the retina, more precisely between the vitreous cortex and the ILM. [13]

While the surface facing the vitreous appears to be smooth over the whole fundus, the retinal surface of the ILM appears differently depending on its location. Peripherally it is relatively smooth similar to the vitreous surface whereas it shows great undulations at the posterior pole that protrude into the nerve fiber layer and the retinal glia.[13]

These undulations have an impact on the thickness of the ILM. While it is uniformly thin in the vitreous base, it progressively and irregularly thickens towards the equatorial and posterior zone. Excepted from this thickening is the foveal zone, where the ILM is the thinnest, and the papillary zone, where the ILM abruptly thins to become the basement membrane of the optic disc.[19]

The vitreous is attached to the retina by fibrils of vitreous cortex that insert into the ILM where they mingle with its fibrillary material.[20] Additionally different matrix-proteins of the ILM seem to work as a extracellular “matrix-glue” contributing to the vitreoretinal interface.[21] The connection between the vitreous body and the retina is generally loose whereby areas of firm attachment do exist.[1] It appears that firm vitreoretinal attachment occurs in areas with a thin ILM such as the vitreous base, the fovea, the peripapillary zone and major retinal blood vessels.[22,23]

1.3.2 Ageing of the vitreous

Aging leads to a progressive aggregation of the fine collagenous fibrils that give the vitreous its gel-like structure at birth. The result of this aggregation is the liquification of the vitreous body.[24]

A study by Bishop et al[25] in 2003 showed that the age-related changes of the vitreous are due to a loss of type IX collagen that shields type II collagen, a fibrillar collagen that tends to fuse on contact. By the loss of its shielding type II collagen is exposed on the fibril surface and therefore predisposed to fuse on contact leading to fibrillar aggregation and weakening of the vitreoretinal adhesion.

By aging the vitreous’ morphology changes progressively from a nearly homogenous structure to a collapsed posteriorly detached vitreous. The only discernible structures in juvenile vitreous are the vitreous cortex and the Canal of Cloquet, a remnant of the hyaloid artery that plays an important role in the embryonic development of the eye.[1,26]

The collapsed, detached vitreous of elderly persons is reduced in its size and shows thickened and tortuous fiber bundles that are distributed throughout the whole vitreous. Cavities filled with liquified vitreous are adjacent to the degenerated fibers.[26]

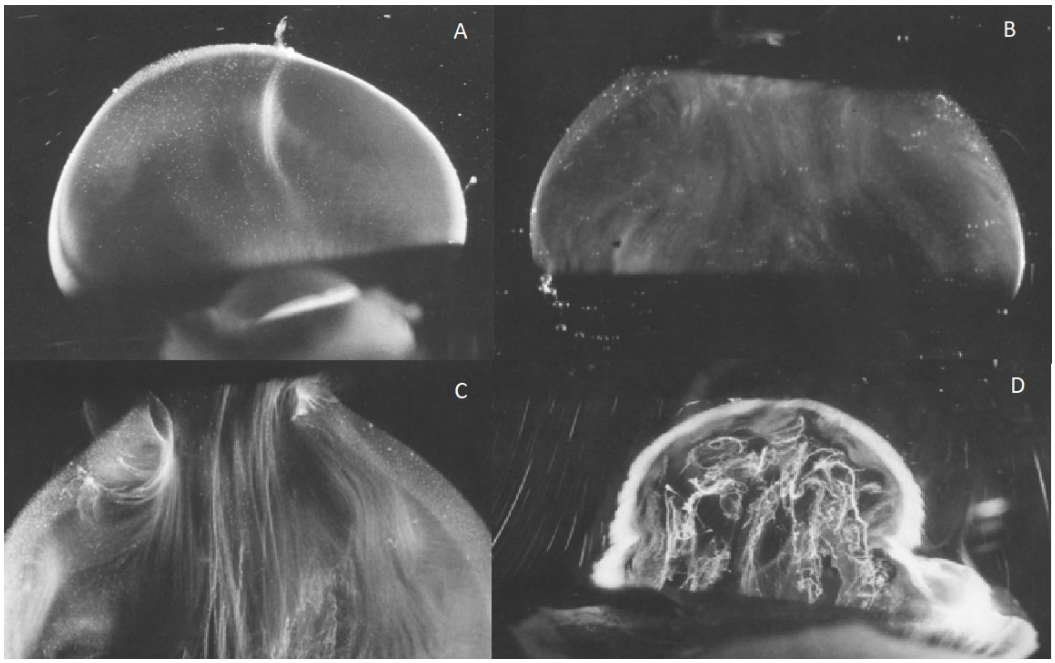

Figure 5: Dark-field horizontal slit illumination images of post mortem dissected vitreous. A: vitreous of a 33-week old embryo. B: vitreous of a 6-year old child. C: vitreous of a 59-year old. D: degenerated vitreous of an 88-year old.[26] Used with the kind permission of Springer Nature.

1.4 VITREOUS HEMORRHAGE

The presence of extravasated blood within the space outlined by the ILM, the nonpigmented epithelium of the ciliary body, the posterior capsule of the lens and the zonula fibers is defined as vitreous hemorrhage, which has an incidence of approximately 7 cases per 100 000.[27,28]

Patients presenting with vitreous hemorrhage claim about visual haze and thereby visual loss, cobwebs, floaters, smoke signals, photophobia and the perception of shadows. On the ophthalmoscopic examination blood is visible within either the vitreous, the retrohyaloid space or the anterohyaloid space or a combination of those.[28]

Hemorrhage within the vitreous differs from hemorrhage in tissues outside of the eye due to unique biochemical features such as rapid clot formation, extracellular lysis of red blood cells, persistence of intact blood cells for months and lack of early polymorphonuclear leukocyte response resulting in a persistence of fibrin.[28]

1.4.1 Causes of vitreous hemorrhage

The main pathological mechanisms leading to vitreous hemorrhage are the disruption of retinal vessels, bleeding from diseased retinal vessels or abnormal vessels and extension of subretinal or intraretinal hemorrhage through the retina. Pathologies underlying a vitreous hemorrhage are proliferative diabetic retinopathy, trauma, retinal tear with or without retinal detachment, retinal vein occlusion, posterior vitreous detachment and Terson's syndrome.[28]

Rare causes are complications of surgical procedures, intraocular tumors, inflammation, vascular lesions, blood disorders, idiopathic conditions and indirect mechanisms such as Valsalva retinopathy, chest compression and shaken baby syndrome.[28]

1.4.1.1 Vitreous detachment with/without retinal tear

As vitreous detachment is part of the vitreous' ageing it is frequently observed. Posterior vitreous detachment (PVD) is more common than a detachment of the anterior or basal vitreous, as the vitreous' connection to its surroundings is more distinct in the latter. Therefore detachment of the anterior or basal vitreous only occurs in the participation of stronger forces as in an ocular trauma.[1]

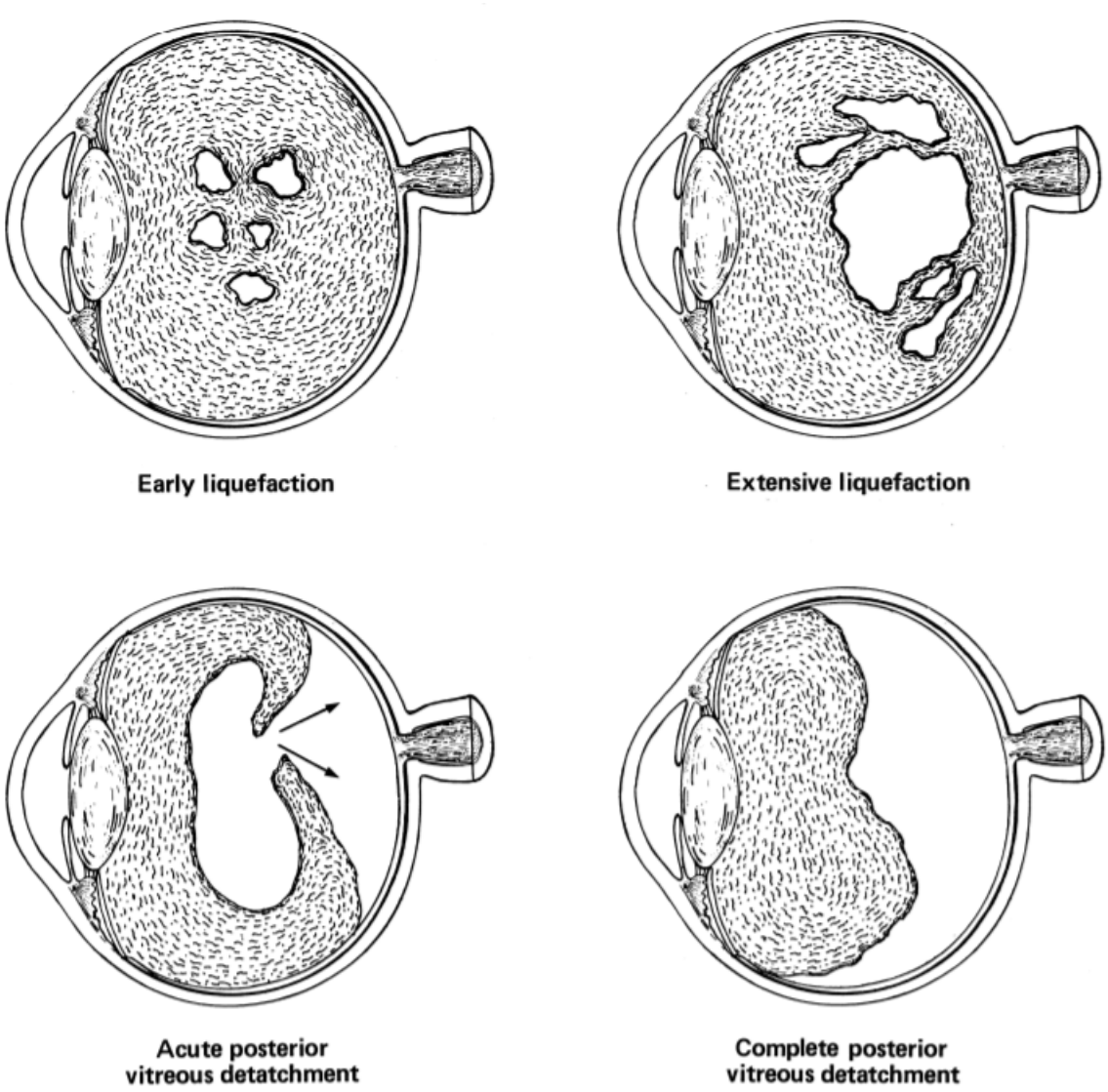

Figure 6: Age-related degeneration of the vitreous body resulting in posterior vitreous detachment.[7] Used with the kind permission of Elsevier.

Spontaneous PVD is seen in 58.4% of patients over the age of 65, in 20.4% between 45 and 65 and in only 4.7% of patients younger than 45, more often bilaterally than unilaterally and more frequently in females than in males.[29] A possible explanation for the unequal distribution between the sexes is the lower concentration of hyaluronate in the female vitreous, supporting its supposed function as a vitreous gel stabilizer.[30] Furthermore, myopic refractive disorders and surgical aphakia are associated with a higher frequency of PVD.[29]

The painless collapse of the vitreous leads to a densification in the vitreous cavity resulting in freely movable opacities that are visible for the patient. These circular or serpentine lines and/or points are called “fleeting flies”, “mouches volantes” or “vitreous floaters”. As the intensity of symptoms differs, some PVDs are not even noticed by the patient.[1]

Complete PVD has to be distinguished from an incomplete PVD in which the vitreous remains to be selectively attached to the retina. Flashes noticed by the patient result from traction by eye movements on these remaining vitreoretinal attachments. If the tractions become too strong they may lead to retinal tears and subsequent retinal detachment or vitreous hemorrhage if vessels are disrupted.[1]

Hence, patients with an incomplete PVD are more likely to experience adverse effects than patients with a complete PVD. These adverse events can develop long after the onset of PVD symptoms.[31]

Up to one fourth of the patients with acute, uncomplicated, symptomatic PVD show an incomplete separation of the posterior vitreous from the retina. Incomplete PVD occurs more often in younger individuals. As the vitreoretinal interface weakens progressively by ageing, a possible explanation for the higher frequency of incomplete PVD in younger patients may be the presence of enhanced vitreoretinal adherence.[31]

The incidence of retinal tears in patients presenting with PVD symptoms is 14.5%, the incidence of vitreous/retinal hemorrhage is reported to be 22.7%. Patients who seek care within the first day of symptoms have a higher incidence of retinal tears than patients who wait after the onset of symptoms. Other predictors of retinal tears are visual impairment at presentation and vitreous/retinal hemorrhage.[32]

1.4.1.2 Retinal detachment

Retinal detachment (RD) is defined as the separation of the neurosensory retina from the underlying RPE. Different kinds of RDs are to be distinguished: rhegmatogenous RD (RRD), tractional RD, combined tractional-rhegmatogenous RD and exudative RD.[6]

In tractional RD the progressive contraction of fibrovascular membranes in large areas with vitreoretinal adhesion leads to retinal separation in the absence of a retinal break. Pathologies leading to this kind of detachment are proliferative retinopathies and penetrating traumata of the posterior segment of the eye.[6]

Exudative RD results from subretinal fluid that derives either from the neurosensory retina or the choroid. It can be observed in different vascular, inflammatory or neoplastic diseases of the neurosensory retina, the RPE and the choroid in which fluid leaks out of blood vessels. As long as the RPE's ability of recirculating fluid into the choroid is sufficiently maintained the retina remains attached. However, if this ability is overstrained or the activity of the RPE is reduced, fluid accumulates in the subretinal space and RD arises.[6]

RRD is the most common form of RD, where a break in the neurosensory retina allows fluid from the liquified vitreous to enter the subretinal space resulting in retinal separation.[33] A retinal break refers to a full-thickness defect in the neurosensory retina. Retinal breaks are either retinal tears that result from PVD and have a predilection for the superior fundus or retinal holes that develop from lattice degeneration. Retinal tears more likely lead to RRD since they are associated with dynamic vitreoretinal traction. Furthermore, superior breaks are more dangerous than inferior ones as gravity leads to a faster spreading of subretinal fluid. Particular caution is required in superior temporal tears as the macula is endangered at an early stage of RRD.[6]

As PVD with retinal tear can result in RRD, symptoms like fleeting flies, flashes and vitreous hemorrhage should be taken seriously and require urgent ophthalmological examination to rule out RRD. Additionally, a visual field defect in case of RD is experienced as a black veil or curtain. As retinal elements project into the opposite visual fields, the retinal defect lies in the opposite quadrant of the visual field defect noticed by the patient. The vision decreases when the subretinal

fluid separates the fovea from the RPE or a large bullous superior RD covers the optical axis.[1,6]

The incidence of RRD is documented to be approximately 1 case per 10 000 inhabitants and reaches its peak in the 6th to 7th decades of life.[34]

Risk factors for RRD are myopic refractive disorder, aphakic eyes, a positive family history for RD and hereditary diseases affecting the collagen-metabolism and therewith the vitreous and the vitreoretinal adherence as Marfan-, Stickler- and Ehlers-Danlos-syndrome.[6,34] Patients with a RRD on one eye have a 100 times greater risk of developing a RRD on the second eye. This risk is higher in male and decreases with age.[35]

In the absence of surgical treatment, RRD progresses and results in complete vision loss in the affected eye.[35] Surgical methods used for reattachment of the retina are pars plana vitrectomy and scleral buckling. The overall success rate is reported to be around 80% after one surgical procedure and is not influenced by the type of operation.[36] The risk of failure is influenced by the presence of preoperative proliferative vitreoretinopathy (PVR) which increases the risk more than twofold and each additional clock-hour of detachment that increases the risk by 13%.[36]

The median visual outcome after RRD surgery is reported to be 0.18-0.5 logMAR and does not significantly differ between scleral buckling and vitrectomy.[37,38] PVR, failure of surgery, extensive RRD, poor presenting visual acuity and pre-operatively detached macula correspond with a poorer visual outcome. In macula-off RRD, patients with a duration of visual symptoms of < 3 days show better visual recovery than patients with a longer duration of symptoms.[37]

PVR is a complication of RD and can be observed in patients that underwent surgery after RRD or ocular trauma but also in patients without vitreoretinal surgery. Identified risk factors for PVR in eyes with RD are giant, large, or multiple tears, signs of uveitis, aphakia, vitreous hemorrhage and preoperative choroidal detachment.[39]

The retinal break allows RPE cells to enter the vitreous cavity. By moving on the retinal surface and developing myofibroblast-like properties they engender the formation of epi- and subretinal membranes, resulting in a contraction of the retinal

surface. In eyes with PVR, retinal reattachment is hampered by the wrinkled retina and the vitreous membranes.[1,6]

PVR starts earliest at two weeks after an event and develops in most cases within the first two month after onset of retinal diseases. The time gap between the event and PVR can be explained by the time RPE cells need to migrate, transform, proliferate and cause subsequent contraction.[40]

1.4.1.3 Retinal vein occlusion

Retinal vein occlusion (RVO) results in an impaired venous return from the retinal circulation. Depending on the site of obstruction RVOs are subdivided into branch retinal vein occlusions (BRVO), hemiretinal vein occlusions (HRVO) and central retinal vein occlusion (CRVO). In CRVO the occlusion lies posterior of or within the optic nerve head whereas the occlusion in HRVO occurs directly at the major bifurcation and any obstruction within a tributary is called BRVO.[41]

The prevalence of BRVO and CRVO increases with age. BRVO affects 4 persons out of 1000 (0.4%) and CRVO affects 0.8 out of 1000 persons (0.08%) which means that approximately 16 million adults worldwide are affected by RVO.[42]

The 15-year cumulative incidence for RVO is reported to be 2.3% (1.8% BRVO and 0.5% CRVO, respectively).[43]

In a large population based German cohort study Ponto et al[44] showed that more than 90% of patients with RVO had one or more cardiovascular risk factors or diseases.

Furthermore, blood pressure, waist-to-hip ratio and BMI are higher in patients with RVO than in patients without RVO. BRVO is highly associated with arterial hypertension and atrial fibrillation and CRVO shows a positive association with age and family history of stroke.[44] Additionally it is reported that diabetes mellitus is associated with RVO and found significantly more often in eyes with CRVO.[45]

RVO can be the first manifestation of undiagnosed arterial risk factors, especially essential hypertension.[46]

Glaucoma history is associated with all three types of RVO. Thus, it is recommended to evaluate patients with RVO for cardiovascular risk factors, diabetes mellitus and glaucoma.[47]

As the risk factors already indicated, atherosclerosis is important in the pathogenesis of RVO. As a retinal arteriole and its corresponding vein have a joint adventitia an atherosclerotic thickening of an anteriorly running arteriole leads to a compression of the underlying vein. The same goes with the central artery and the central vein sharing an adventitia posterior of the lamina cribrosa. The obstruction leads to secondary changes such as loss of venous endothelial cells, clot formation and occlusion.[6]

The occlusion of a retinal vein entails an increase of venous and capillary pressure and a stagnation of circulation resulting in hypoxia of the retinal area that is supposed to be drained by the closed vein. Hypoxia in turn leads to a damage of capillary endothelial cells and an extravasation of blood components. Tissue pressure increases and intensifies the stagnation of circulation as well as hypoxia, creating a vicious circle.[6]

Interrupted blood flow holds the risk of many complications harming the patient's vision such as macular edema, macular ischemia, optic neuropathy, vitreous hemorrhage, or tractional RD. Yet symptoms can be subtle or even non-existent if the severity is mild or the area affected by the occlusion does not involve the macula.[41]

Vitreous hemorrhage in eyes with RVO originates either from breakthrough of congestion or from newly built, fragile vessels in case of ischemia-induced neovascularization which carries an unfavorable visual prognosis. Hypoxia and capillary nonperfusion lead to an upregulation of cytokines including vascular endothelial growth factor (VEGF) and therefore to an increased vascular permeability and neovascularization. This abnormal blood vessel growth can be observed on the iris, the anterior chamber angle, the optic nerve and the retina.[41]

1.4.1.4 Terson's syndrome

Terson's syndrome describes a vitreous hemorrhage in combination with a subarachnoid hemorrhage caused by an aneurysm rupture.[6,48]

Intraocular hemorrhage associated with subarachnoid hemorrhage occurs within the vitreous, the subhyaloid space, sub-ILM, intraretinal and in subretinal spaces although the strict definition of Terson's syndrome only describes vitreous hemorrhage.[48,49]

The intraocular hemorrhage is supposed to result from a retinal venous stasis following increased pressure in the cavernous sinus.[6]

The frequency of vitreous hemorrhage in patients with subarachnoid hemorrhage differs between prospective and retrospective studies and is reported to be 13% and 3% respectively, suggesting that vitreous hemorrhage is not well documented. Even though the occurrence of vitreous hemorrhage in patients with subarachnoid hemorrhage is reported to be an adverse prognostic finding.[48]

Factors associated with Terson's syndrome are aneurysm size, World Federation of Neurosurgical Societies (WFNS) scale (combining Glasgow Coma Scale with motoric deficits) at admission and the method of operation. Therefore, ophthalmologic examination is suggested to be performed in every patient with an aneurysm size of over 5mm and/or a WFNS score over 4 (equivalent to a Glasgow Coma Scale score between 3 and 12). Additionally, further ophthalmologic examination should be taken into consideration in patients that underwent endovascular coil embolization.[50]

1.4.2 Diagnosis and Management

Anterior slit-lamp examination, fundus examination, measurement of intraocular pressure (IOP) and ocular ultrasound (US) are the main diagnostic features to determine the underlying cause of vitreous hemorrhage.[51]

Anterior slit-lamp examination should be performed with a focus on anterior chamber angle or iris neovascularization that suggest neovascular Etiology. Presence of keratic precipitates and cells in the anterior chamber indicate inflammatory Etiology. Fundus examination of the affected eye is often impossible due to dense hemorrhage. Evaluation of the fellow eye can help to determine the cause of hemorrhage in the affected eye.[51]

In fundus obscuring vitreous hemorrhage, a US B-scan with corresponding A-scan is needed to detect mass lesions or RD. Emphasis should be on the vitreous cavity, the vitreoretinal interface and the retinochoroidal layer.[51]

Optical opacities within the vitreous cavity generate echoes of varying amplitudes. The visualization of these varying amplitudes in US helps to diagnose PVD, retinal tears and RD in eyes with vitreous hemorrhage. A retinal tear is displayed as two intense echo tags with a drop in the retinal level posterior to them. While PVD appears as a faint line in US B-Scan without vitreous hemorrhage, the outline of the posterior hyaloid interface can be clearly delineated in the presence of vitreous opacities, such as blood. In contrast to PVD, in which only one interface can be imaged, two interfaces should be visible in case of RD, one from the detached retina and from the PVD.[52]

Ruling out severe causes for vitreous hemorrhage in the US is crucial to plan the treatment and help with estimating the potential visual outcome.[51]

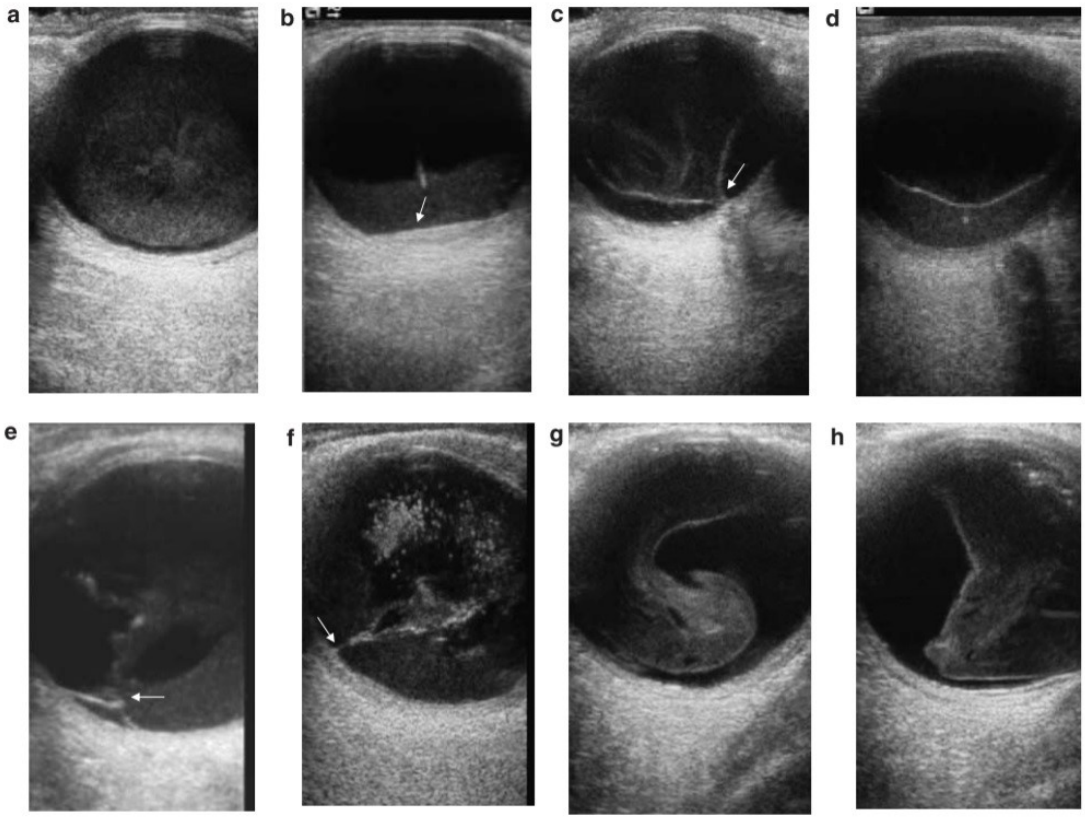

Figure 7: B-Scan ultrasound of vitreous hemorrhage. a: Intragel hemorrhage with PVD. b: retrohyaloid hemorrhage with PVD. c: intragel and retrohyaloid hemorrhage with incomplete PVD. d: intragel and retrohyaloid hemorrhage with PVD. e: deviated gaze; temporal retinal tear with retrohyaloid and central gel hemorrhage (clear cortical gel). f: deviated gaze; asteroid hyalosis with retrohyaloid hemorrhage and vitreoretinal adhesion at site of a BRVO. g: laterally deviated gaze: movement of intragel hemorrhage. h: same eye as in g; nasally deviated gaze; movement of intragel hemorrhage.[52] Abbreviations: PVD= posterior vitreous detachment; BRVO= branch retinal vein occlusion. Used with the kind permission of Springer Nature.

The measurement of IOP is mandatory. If the pressure is less than 9 mmHg or more than 22 mmHg investigation and explanation are needed. Pressure lowering reasons of vitreous hemorrhage are RD, wound leak or an open globe injury. Hypertonia would suggest the presence of a neovascular glaucoma, hemolytic glaucoma, corticosteroid usage or tumor invasion.[51]

Treatment and management options do vary, depending of the underlying cause of vitreous hemorrhage. Common treatment options are observation, laser photocoagulation, cryotherapy and vitrectomy.[51]

As blood within the vitreous cavity often clears within days to weeks, observation is a regular treatment method in eyes without detected retinal breaks and/or detachment in US.[51]

Blood within the retrohyaloid space, as present in eyes with PVD, resorbs faster than blood within the vitreous gel. Therefore, patients are asked to position their head vertically and reduce eye movements to accelerate the settlement of blood in this space and prevent blood from entering the vitreous gel through holes that develop in the hyaloid membrane.[53]

Revaluation within 3 to 7 days to ascertain the source of hemorrhage is recommended. As soon as the underlying pathology is known and RD is ruled out revaluation is done after a period of 3-4 weeks.[51]

1.5 VITRECTOMY

The surgical removal of the vitreous is called pars plana vitrectomy. Timing for this surgery is crucial. While observation is reasonable in a lot of cases and delayed vitrectomy is the established treatment method in eyes with persisting hemorrhage, some cases require an early surgical intervention to prevent the underlying pathology from progression.[28,51] Verified RD in ultrasonography is an indication for early surgery. In the absence of an urgent indication, other factors such as associated diseases, risk of surgery and informed preference of the patient must be taken into consideration in the decision of management.[54]

First performed by Robert Machemer in 1970 pars plana vitrectomy developed and improved in the last decades from a long and dangerous operation to a controlled and standardized surgical procedure.[55]

1.5.1 Technique and instruments

Main instruments used are the vitreous cutter, an intraocular light source and an infusion cannula that are inserted into the vitreous cavity through three sclerotomies above the pars plana of the ciliary body, 3.5-4mm posterior of the limbus (3.5mm in pseudophakic or aphakic eyes; 4mm in phakic eyes) as perforation of the eyeball is safe in this area and should not cause RD. All instruments have the same shaft diameter and can therefore be exchanged and inserted in any of the scleral ports.[2,6] 19-gauge and 20-gauge instruments were used for three port-vitrectomy until 25-gauge instruments were introduced by Fuji et al[56] in 2002. 27- and 23-gauge systems were added afterwards. These newer small gauge instruments have the advantage of smaller ports which don't need to be sutured and smaller instrument ends which allow safer and more precise work close to the retina.[55]

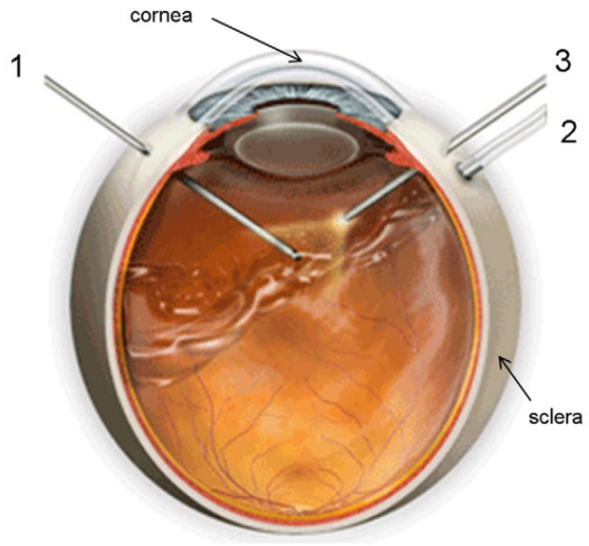

Figure 8: Pars Plana Vitrectomy. 1=vitreous cutter 2=infusion cannula 3=light source.[57] Used with the kind permission of Elsevier.

After fixating the infusion cannula in the lower sclerotomy at the inferior margin of the lateral rectal muscle the vitreous cutter and the fiberoptic are inserted into the upper ports at 2 and 10 o'clock. The vitreous gel and the posterior hyaloid membrane get cut and aspirated by the vitreous cutter which is oscillating up to 6000 times a minute. Physiological saline solution is supplied through the infusion cannula to ensure constant IOP while the vitreous is excised. The surgeon who gains insight through the pupil by the surgical microscope is controlling the cutting speed and the suction power with a foot pedal. If demanding cases require bimanual surgery the light source can be inserted in a self-fixating cannula through a fourth sclerotomy so that the surgeon can use additional instruments.[2,6]

1.5.2 Complications

The continuing evolution of surgical technique, indications and instruments lead to an improvement of visual and anatomical outcomes of vitrectomy. As the number of performed PPVs nearly doubled in the USA from 1995 to 2005 and it is estimated that there are 500 000 patients worldwide undergoing this surgery every year it is important to mention the potential adverse events.[58]

A review of claims data in the USA by Stein et al[59] included around 13500 elderly patients that underwent PPV from 1994 to 2006 and provides an insight in the complication rates and their change over time.

Severe complications are endophthalmitis, suprachoroidal hemorrhage and RD. Less severe adverse events include choroidal detachment, vitreous hemorrhage, retinal edema, glaucoma, retinal tear, hypotony, corneal edema and recurrent corneal abrasion/erosion. While rates of severe sight threatening complications after vitrectomy are relatively low and have not changed between 1994 and 2006, with an incidence ranging between 4.8 and 5.5%, less severe complications were found to be significantly higher in the 2006 cohort (20%) than in the 1994 (17.3%) and 1999 cohort (14.8%). The same goes with the need for additional operations. A possible explanation for this increase is the improvement of diagnostic imaging devices and therefore an increased ability of detecting certain retinal conditions.[59]

Despite the improved diagnostic capabilities cases of unexpected vision loss after vitrectomy remain. This may be explained by the toxicity of chemical substances used for intraocular staining and tamponade.[60]

1.5.3 Tamponades

In some cases a tamponade is required to ensure retinal attachment.[2]

The purpose of the tamponade is to form a barrier that prevents vitreous fluid from getting into the subretinal space.[61]

As vitreous substitutes are topic of research for many years now, a variety of tamponades, including inert gas, silicon oil, heavy silicon oil and hydrogel, is available. Most commonly used in clinical practice are the gases octafluoropropane (C3F8) and sulfur hexafluoride (SF6) as well as silicon oil with a viscosity of either 1000 or 5000 centistokes (CS).[57,62]

1.5.3.1 Silicon oil tamponade

Invented in the 1960s and widely spread in the 1980s latter is still the only material available for long term vitreous substitution although it may induce several clinical complications.[57]

Silicone oil has the benefit of keeping most of its transparent structure indefinitely within the vitreous cavity and has an extended retinal tamponade activity. As silicone oil has a lower density than water or aqueous solutions it floats upon residual liquified vitreous resulting in a reduced or missing tamponade effect for inferior retinal breaks.[57]

Fluorosilicone liquids, better known as heavy silicone oils, are heavier than water and thus able of discharging subretinal fluids out of breaks in the periphery and of tamponing inferior retinal breaks.[63,64]

Although silicone oils are well tolerated in most eyes, complications like cataract, keratopathy, pupillary block glaucoma, fibrous epiretinal and subretinal proliferations and pain lead to lingering criticism.[57,65]

Several lines of evidence support the supposition that the complications are not caused by intrinsic silicone oil toxicity but by the property of emulsified silicone oil to penetrate ocular tissues resulting in abnormal cell behavior as cells may incorporate silicone oil vesicles.[57,63]

The injection of non-emulsified silicone oil into rabbit's eyes showed no histological changes of the retina. In eyes with emulsified silicone oil instillation on the other hand penetration of the inner retina was found after one week and epiretinal membrane formation, similar to silicone oil retinopathy, was present after four weeks.[66]

In most eyes silicone oil emulsification starts within the first year after instillation, ranging from 5 to 24 months.[67] The decision of when to remove the silicone oil is up to the surgeon's discretion. In demanding cases silicone oil removal can be postponed up to one year postoperatively if a close monitoring of emulsification signs can be ensured.[67]

Heavy silicone oil is assumed to have a tendency to emulsify to an even greater extent than regular silicone oils.[68]

Therefore it is recommended to use silicone oil only in severe cases and only temporally as it still is the most biocompatible material for long time vitreous substitution.[63]

1.5.3.2 Gas tamponade

Air was the first gas to be injected into the eye. Due to its short resistance time of only a few days, its benefit as a tamponade is minimal. In the early days of PPV surgeons began to use expanding gases.[57]

SF6 and C3F8 are the most commonly used gases. The former in a concentration of 30% has a longevity of 18 days with a standard deviation (SD) of 2.6 days, the latter in a concentration of 20% a longevity of 34.5 days with a SD of 3.3 days.[69]

These gases owe their expansion and therewith longer intraocular residence time to the diffusion of other gases from the bloodstream.[70]

The expansive gases need to be instilled in adequate dosages since their expansion can elevate the IOP. In addition, it is mandatory to inform the patients to avoid high-altitude travel and nitro oxide anesthesia as long as the gas is not resolved because the gas may additionally extent under these circumstances.[60]

Due to the physical properties of gas, the patients need to position themselves adequately in order to achieve a benefit from gas. In detail, prone positioning is recommended for patients with RD or macula hole who underwent vitrectomy with gas tamponade in order to tamponade the posterior pole of the retina. Due to the arduousness of this positioning the patient compliance is inconsistent.[64,71]

2 STUDY

2.1 PURPOSE

Vitreous hemorrhage is a common cause for visual loss with various underlying diseases.

While a conservative approach might be reasonable, some patients require vitrectomy which can be performed either early or delayed. The timing of the surgery depends on individual factors, the danger of the underlying disease's progression and the persistence of vitreous hemorrhage.

While most studies concerning vitrectomy-requiring vitreous hemorrhage were performed in eyes with proliferative diabetic retinopathy (PDR), little is published about the causes and the timing of vitrectomy in eyes without PDR.

Thus, the aim of this study is to assess the etiology, the timing of vitrectomy and the visual development in eyes of non-diabetic patients who underwent first time vitrectomy at the Department of Ophthalmology, Medical University of Graz in the period from 2000 to 2015.

A further objective of this work is to find out if the timing of vitrectomy has an influence on the visual development and if the causes leading to vitreous hemorrhage are distributed equally between the early and the delayed vitrectomy group.

2.2 PATIENTS AND METHODS

A retrospective data analysis was performed on non-diabetic patients with the main diagnosis code of vitreous hemorrhage, who underwent first-time vitrectomy in the period from 2000 to 2015 (15 years) at the Department of Ophthalmology, Medical University of Graz.

Diagnosis of PDR or diabetes mellitus and a previous vitrectomy on the affected eye were applied as exclusion criteria.

After application of the exclusion criteria the medical records of the remaining 161 eyes of 158 patients were reviewed by use of EyMed. EyMed is a FileMaker based clinic system for documentation and quality assurance used at the Department of Ophthalmology, Medical University of Graz.

Main outcome measures included the cause of vitreous hemorrhage, the visual development and the timing of vitrectomy, whereby a vitrectomy within 30 days after initial presentation was defined as early vitrectomy and any vitrectomy after that period as delayed vitrectomy. In addition, the causes of vitreous hemorrhage and the visual development were evaluated for the early and the delayed vitrectomy group and subsequently compared among each other.

Visual acuity data was analyzed at three different dates: at initial presentation, preoperatively and the best corrected visual acuity (BCVA) in a follow-up time of up to two years. BCVA was not included into analysis if there was no presentation within two years postoperatively or if there was no presentation between vitrectomy and re-vitrectomy, post-operative bleeding or post-operative RD.

Furthermore, patients with visual acuity decreasing conditions not related to vitreous hemorrhage, including age-related macular degeneration (AMD), macular edema, macular atrophy, optic nerve damage and a central scar were excluded from visual acuity analysis.

Visual acuity was documented in decimal and converted into the logarithm of the minimum angle of resolution (logMAR) for statistical analysis.

Data was collected in Microsoft Excel (Microsoft Corporation, Redmond, WA) and statistically analyzed in SPSS Statistics 25 (IBM Corporation, Armonk, NY).

Descriptive statistics were used to summarize data. Continuous data were presented as mean ± standard deviation (SD). Comparison between the early and delayed vitrectomy group was performed by using Fisher's exact test (for binary variables) and two-sided Student's t-test for unpaired samples (for continuous variables).

Analysis of the visual acuity development within each group was performed with the two-sided Student's t-test for paired samples.

A p-value less than 0.05 was considered as significant.

2.3 RESULTS

2.3.1 Timing of vitrectomy and patients' characteristics

Of the 161 eyes included in this study, the time between initial presentation and vitrectomy was determined in 160 cases, due to one patient having no documented presentation prior surgery.

The mean time between initial presentation and vitrectomy in the 160 eyes was 65.1 ± 65.7 days.

Early Vitrectomy was performed in 74 eyes (46.5%), while 86 eyes (53.7%) underwent delayed vitrectomy.

In the early vitrectomy group, the average time to surgery was 12.8 ± 9.2 days, compared to 93.3 ± 70.6 days in the delayed vitrectomy group.

79 patients were male (50%) and 79 patients female (50%). Mean age was 68.0 years ± 16.6 years, ranging from 7 to 95 years. 82 patients (51.9%) were diagnosed with arterial hypertension. At the time vitreous hemorrhage occurred 38 eyes (23.6%) were pseudophakic.

There was no significant difference in terms of age, hypertension and phakic status between the early and the delayed vitrectomy group. The only significant difference found was gender (Table 1), as female patients were more frequently found in the early vitrectomy group compared to male patients.

	Early VE (n=74)	**Delayed VE (n=86)**	**p**
Age (years), mean (SD)	65.5 ± 19.5	70.3 ± 13.5	0.078
Hypertension, *n*	35	41	1.00
Lens status, *n*			0.264
Pseudophakic	21	17	
Phakic	53	69	
Gender, *n*			**0.041**
Male	30	49	
Female	44	37	

Table 1: Comparison of the patient characteristics between the early and delayed vitrectomy group. Abbreviations: SD= standard deviation; VE= vitrectomy; p= p-value.

2.3.2 Tamponades

Vitrectomy without tamponade was performed in 68 cases (42.2%).

In 50 eyes (31.1%) gas was used as tamponade and in 43 eyes (22.7%) silicone oil.

In 34 eyes (68% of the eyes with gas tamponade and 21.1% of the total number) air was the substance used. SF6 was used in 12 eyes (24% of the eyes with gas tamponade and 7.5% of the total number) and C3F8 in four eyes (8% of the eyes with gas tamponade and 2.5% of the total number)

Silicone oil with a viscosity of 1000 CS was the most commonly used silicone oil tamponade and was applied in 32 eyes (74.4% of the eyes with silicon oil tamponade and 19.9% of the total number). Silicone oil with 5000 CS was used in 11 eyes (25.6% of the eyes with silicone oil tamponade and 6.8% of the total number).

	Total (n=161)
Vitrectomy without tamponade, *n (%)*	68 (42.2%)
Vitrectomy with gas tamponade, *n (%)*	50 (31.1%)
Air	34 (21.1%)
SF6	12 (7.5%)
C3F8	4 (2.5%)
Vitrectomy with silicon oil tamponade, *n (%)*	43 (26.7%)
Silicon oil 1000CS	32 (19.9%)
Silicon oil 5000CS	11 (6.8%)

Table 2: Tamponade used. Abbreviations: SF6= sulfur hexafluoride; C3F8= octafluoropropane; CS= centistokes.

2.3.3 Etiology

2.3.3.1 Overall Etiology

The most common cause for vitreous hemorrhage found in this study was RVO with 44 eyes (27.3%).

BRVO was diagnosed in 25 eyes (56.8% of the eyes with RVO and 15.5% of the total number), CRVO in 16 eyes (36.4% of the eyes with RVO and 10.6% of the total number) and HRVO in three eyes (6.8% of the eyes with RVO and 1.9% of the total number).

Retinal tear with and without RD caused vitreous hemorrhage in 31 cases (19.3%). In a total of 19 eyes (11.8%) RD was detected compared to 12 eyes (7.5%) that showed a retinal tear without RD. PVD without retinal tear was the reason for vitreous hemorrhage in 14 eyes (8.7%).

Further causes included Terson's syndrome with 8 eyes (5%), ocular trauma with 5 eyes (3.1%) and operative complications with 7 eyes (4.3%).

57.1% (four cases) of the operative complications were associated with cataract surgery and 14.3% (one case) with scleral buckling, cerclage and intravitreal drug injection (IVI), respectively.

Branch (BRAO) and central (CRAO) retinal artery occlusion caused vitreous hemorrhage in three eyes (1.9%), two and one respectively. In another three eyes (1.9%) a choroidal detachment was determined as the underlying cause of vitreous hemorrhage and in two eyes (1.2%) an intraocular lymphoma.

In one eye vitreous hemorrhage was caused by polycythemia vera (0.6%) and in one eye a retinal macroaneurysm (0.6%) was identified as the source of hemorrhage. Furthermore, there was one case of radiation retinopathy (0.6%) and one case of intermediate uveitis (0.6%).

In 40 cases (24.8%) the cause remained unknown.

Cause	Total (n=161)
Unknown, *n (%)*	40 (24.8%)
Retinal tear with retinal detachment, *n (%)*	19 (11.8%)
Retinal tear without retinal detachment, *n (%)*	12 (7.5%)
RVO, *n (%)*	44 (27.3%)
BRVO	25 (15.5%)
CRVO	16 (10.6%)
HRVO	3 (1.9%)
PVD, *n (%)*	14 (8.7%)
Terson's syndrome, *n (%)*	8 (5.0%)
Trauma, *n (%)*	5 (3.1%)
Operative complication, *n (%)*	7 (4.3%)
Cataract surgery	4 (2.5%)
Scleral buckling	1 (0.6%)
Cerclage	1 (0.6%)
IVI	1 (0.6%)
Miscellaneous, *n (%)*	12 (7.5%)
BRAO	2 (1.2%)
CRAO	1 (0.6%)
Uveitis intermedia	1 (0.6%)
Polycythemia vera	1 (0.6%)
Choroidal detachment	3 (1.9%)
Retinal makroaneurysm	1 (0.6%)
Intraocular lymphoma	2 (1.2%)
Radiation retinopathy	1 (0.6%)

Table 3: Causes of vitreous hemorrhage. Abbreviations: RVO= retinal vein occlusion; BRVO= branch retinal vein occlusion; CRVO= central retinal vein occlusion; HRVO= hemiretinal vein occlusion; PVD= posterior vitreous detachment; IVI= intravitreal drug injection; BRAO= branch retinal artery occlusion; CRAO= central retinal artery occlusion.

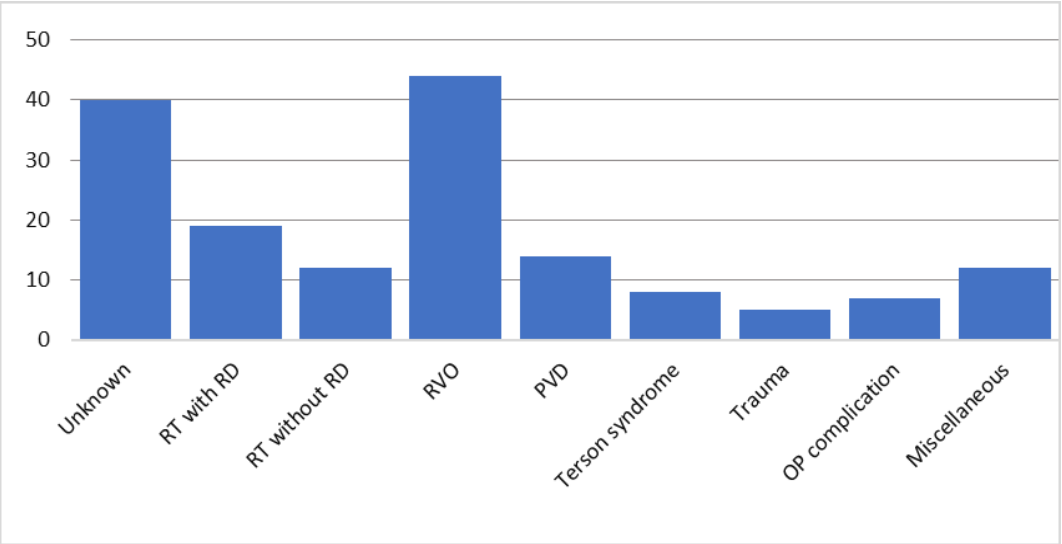

Figure 9: Causes of vitreous hemorrhage. Abbreviations: RT= retinal tear; RD= retinal detachment; RVO= retinal vein occlusion; PVD= posterior vitreous detachment; OP= operative.

2.3.3.2 Etiology by timing of vitrectomy

Operative complications (7 eyes) and ocular trauma (5 eyes) were the only causes that exclusively underwent early vitrectomy ($p = 0.004$ and $p = 0.02$, respectively).

In eyes that sustained ocular trauma, surgery was performed at an average of 18 ± 8.6 days after initial presentation. In eyes with vitreous hemorrhage due to an operative complication the average time to vitrectomy was 5.1 ± 3.1 days.

From a total of 19 eyes with detached retina, 15 eyes underwent vitrectomy within 30 days after initial presentation compared to 4 eyes that underwent surgery beyond that period. The difference is statistically significant (p-value = 0.003). Average time to surgery was 21.8 days ± 22.0 days.

While early vitrectomy appeared to be more frequently performed in case of retinal tears without RD, delayed vitrectomy tended to be more frequently performed in eyes with unknown causes, PVD, RVO and Terson's syndrome. However, the differences were not statistically significant.

There were no causes that significantly more often underwent vitrectomy beyond 30 days after initial presentation.

Cause	**Early VE** (n= 74)	**Delayed VE** (n= 86)	P
Unknown, *n (%)*	15 (20.3%)	25 (29.1%)	0.272
RT with RD, *n (%)*	15 (20.3%)	4 (4.7%)	**0.003**
RT without RD, *n (%)*	7 (9.5%)	5 (5.8%)	0.283
PVD, *n (%)*	4 (5.4%)	10 (11.6%)	0.261
RVO, *n (%)*	15 (20.3%)	28 (32.6%)	0.107
Terson's syndrome, *n (%)*	2 (2.7%)	6 (7.0%)	0.288
Trauma, *n (%)*	5 (6.8%)	0 (0.0%)	**0.020**
OP complication, *n (%)*	7 (9.5%)	0 (0.0%)	**0.004**
Miscellaneous, *n (%)*	4 (5.4%)	8 (9.3%)	0.386

Table 4: Causes of vitreous hemorrhage by timing of vitrectomy. Comparison of the number of causes that led to vitreous hemorrhage in the early and delayed vitrectomy group. Statistical analysis was performed with Fisher's exact test. Abbreviations: RT= retinal tear; RD= retinal detachment; RVO= retinal vein occlusion; PVD= posterior vitreous detachment; OP= operative.

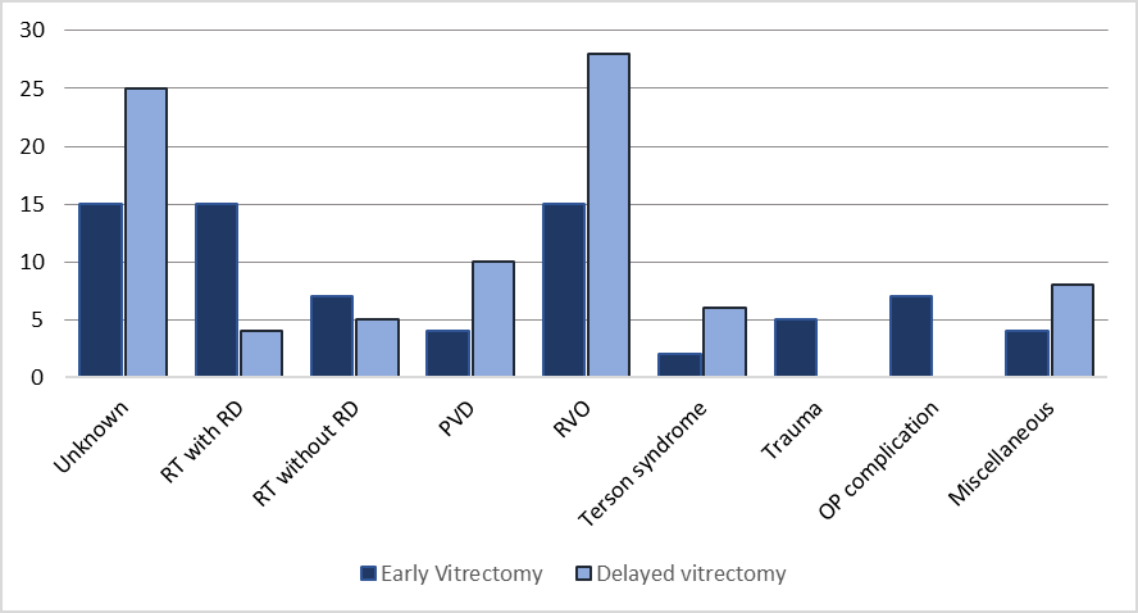

Figure 10: Causes of vitreous hemorrhage by timing of vitrectomy. Abbreviations: RT= retinal tear; RD= retinal detachment; RVO= retinal vein occlusion; PVD= posterior vitreous detachment; OP= operative.

2.3.4 Visual acuity

Due to visual acuity decreasing conditions unrelated to vitreous hemorrhage, 48 eyes were excluded from visual acuity analysis.

One case was excluded because of no documented presentation prior surgery, whereby an allocation to the early or the delayed vitrectomy group was unfeasible.

In another 4 cases visual acuity was not documented at initial presentation. Preoperative and final BCVA was missing in one and 56 cases, respectively.

Hence, visual acuity data was applicable in 108 eyes at initial presentation, in 111 eyes preoperatively and in 56 eyes for the final BCVA. Follow up time was 9.1 ± 6.4 months.

Mean visual acuity at initial presentation was 1.89 ± 0.78 logMAR and mean preoperative visual acuity was 1.98 ± 0.79 logMAR. There was no significant change of visual acuity between these two dates ($p=0.252$). After vitrectomy the final BCVA was 0.92 ± 0.86 logMAR ($p<0.001$).

There was no significant difference between the early and the delayed vitrectomy group in terms of visual acuity at initial presentation (2.03 ± 0.73 logMAR and 1.78 ± 0.81 logMAR, respectively; $p = 0.099$).

Preoperative visual acuity was significantly worse in the early vitrectomy group compared to the delayed vitrectomy group (2.17 ± 0.61 logMAR and 1.84 ± 0.79 logMAR, respectively; $p = 0.015$).

The comparison of the preoperative and the final BCVA showed that vitrectomy significantly improved visual acuity in both groups ($p<0.001$).

The early and the delayed vitrectomy group showed equal results in terms of final BCVA (0.79 ± 0.74 logMAR and 1.03 ± 0.95 logMAR, respectively; $p = 0.29$).

Timing of Vitrectomy	Initial presentation	Preoperative	P
Early (n=49)	2.01 ± 0.73	2.16 ± 0.61	0.196
Delayed (n=58)	1.78 ± 0.81	1.82 ± 0.81	0.703
Total (n=107)	1.88 ± 0.78	1.97 ± 0.74	0.252
	Preoperative	**Final BCVA**	
Early (n=26)	2.34 ± 0.51	0.79 ± 0.74	**<0.001**
Delayed (n=30)	1.92 ± 0.69	1.03 ± 0.95	**<0.001**
Total (n=56)	2.11 ± 0.64	0.92 ± 0.86	**<0.001**

Table 5: Visual acuity development of the early and the delayed vitrectomy group. Top half of the table shows the difference of the mean visual acuity between initial presentation and preoperative in total and for each group. Bottom half of the table shows the difference between the mean preoperative visual acuity and the final BCVA for each group and in total. Statistical analysis was performed with student's t-test for dependent samples. Due to the difference in the number of documented visual acuity data in both halves of the table the mean preoperative visual acuity differs between the top and the bottom half of the table. Abbreviations: VE= vitrectomy; p= p-value; IP= initial presentation; preOP= preoperative; BCVA= best corrected visual acuity.

	Total	Early VE	Delayed VE	p
Initial presentation (n=108)	1.89 ± 0.78	2.03 ± 0.73	1.78 ± 0.81	0.099
Preoperative (n=111)	1.98 ± 0.73	2.17 ± 0.61	1.84 ± 0.79	**0.015**
Final BCVA (n=56)	0.92 ± 0.86	0.79 ± 0.74	1.03 ± 0.95	0.29

Table 6: Visual acuity comparison between the early and the delayed vitrectomy group. Comparison of the mean visual acuity in logMAR between both groups for all three dates. For statistical analysis student's t-test for two independent samples was used. Abbreviations: VE= vitrectomy; p= p-value; IP= initial presentation; preOP= preoperative; BCVA= best corrected visual acuity.

3 DISCUSSION

Manifold pathologies can be causative for the presence of extravasated blood within the vitreous cavity. A major review by Grossniklaus et al[28] showed that in the mean of six studies PDR was the most common etiology of vitreous hemorrhage, followed by retinal tears with or without RD and RVOs. Leaving PDR aside, as diabetic patients were excluded from this study, the etiologies found in our work resemble largely the findings of other studies.[27,72]

With 27.7% RVO was the leading cause found in this study, followed by retinal tears with RD (11.8%) and retinal tears without RD (7.5%). In most etiological studies on vitreous hemorrhage, the retina remained more often attached in case of a retinal tear.[27,73] As stated above our findings are contrary. This can be explained by the inclusion criteria applied, as we solely analyzed eyes with vitreous hemorrhage that required vitrectomy.

In 24.8% of the eyes included in this study the etiology of vitreous hemorrhage could not be assessed, which can partly be explained by the study's retrospective design. In a prospective etiological study, the cause of vitreous hemorrhage was reported to be unknown in 4%.[27] Furthermore, it can be assumed, as Verbraeken et al[74] did in a study similar to this one, that in a majority of the cases with unknown etiology PVD was causative for vitreous hemorrhage, as no pathological characteristics were documented. PVD without retinal tear was explicitly documented in 8.7% of the eyes included in this study. Further cases in which no cause was determined may possibly be explained by exudative AMD. In contrast to some other studies[28,74] AMD was not taken into the list of possible causes in this work as AMD was documented as a further eye disease and an unequivocal relation between AMD and vitreous hemorrhage could not be established in any of the cases. Even so, it can be presumed that in some of the eyes in which no cause was determined AMD was the underlying disease. The major review by Grossniklaus et al[28] reported that AMD is causative for vitreous hemorrhage in 2% of the eyes. Verbraeken et al[74], who also focused exclusively on the etiology of vitreous hemorrhage in eyes that underwent vitrectomy, reported an incidence of even 13.5%.

While several studies dealt with the timing of vitrectomy and the comparison between early and delayed vitrectomy in eyes with diabetic retinopathy[75,76], little is published about these issues in non-diabetic patients. However, in studies dealing with that topic in non-diabetic eyes, main emphasis was mostly on eyes with retinal tears or at least presumptive retinal tears and early vitrectomy.[54,77]

This study on the contrary focused on the timing of vitrectomy in non-diabetic patients, regardless of whether a retinal tear was present or not. The results show that, waiving the cause of vitreous hemorrhage, the mean time between initial presentation and vitrectomy in non-diabetic patients presenting with vitreous hemorrhage was 65.1 ± 65.7 days. Vitrectomy within 30 days after initial presentation was performed in 46.2% compared to 53.7% that underwent surgery beyond that period. Mean time to surgery in the early group was 12.8 ± 9.2 days and in the delayed group 93.3 ± 70.6 days.

Unsurprisingly, in eyes with RD vitrectomy was significantly more often performed early, as an early surgical intervention is recommended.[78,79] Even so, in four eyes with RD vitrectomy was performed more than 30 days after initial presentation. However, that does not necessarily mean that in these cases RD had to be present for that period. It can reasonably be assumed that in these patients RD was ruled out in B-scan ultrasonography at initial presentation with vitreous hemorrhage and vitrectomy was then indicated when a detached retina occurred and was diagnosed in the follow-up.

In eyes with retinal breaks and attached retina, no significant difference in the timing of vitrectomy was found. These results comply with the preferred practice pattern of the American Academy of Ophthalmology[80] that states that in eyes with vitreous hemorrhage and a suspected retinal tear a conservative approach with repeated US examination should be followed. Taking this into consideration it can be presumed that in eyes with a detected retinal break that underwent delayed vitrectomy a conservative approach was followed, and vitrectomy was eventually performed because a spontaneous resolution of the hemorrhage did not occur.

Feng et al[81] recommend early surgical intervention in eyes with vitreous hemorrhage caused by ocular trauma, as the presence of vitreous hemorrhage in these eyes is reported to be a high risk factor for the development of PVR. Corresponding to this finding, patients with ocular trauma exclusively underwent

early surgery in our study. In patients with vitreous hemorrhage as an adverse event of eye surgery vitrectomy was also exclusively performed early.

As recommended[82], vitrectomy tended to be performed late in eyes with vitreous hemorrhage caused by PVD without retinal tear, RVO and Terson's syndrome.

If the cause of vitreous hemorrhage was unknown there was also a tendency to delayed vitrectomy. These results are in accordance with the findings of a survey performed in Great Britain and Ireland, in which vitreoretinal specialists considered US examination and frequent monitoring essential in eyes with vitreous hemorrhage without obvious cause and tended to perform vitrectomy at a mean of 9.2 weeks after initial presentation.[83]

However, it must be noted that also in regard to the timing of vitrectomy the retrospective aspect of this study has to be taken into account. Thus, it has to be considered that in some cases the symptoms of vitreous hemorrhage may have persisted for weeks or months until medical care was sought. As we defined the timing of vitrectomy as the interval between documented initial presentation and vitrectomy, these patients were assigned to the early vitrectomy group although vitreous hemorrhage may have been present for months.

Surgical intervention improved vision significantly. While the mean visual acuity at initial presentation was 1.89 logMAR, the final BCVA was 0.92 logMAR. Even though we excluded patients with major visual acuity decreasing conditions not related to vitreous hemorrhage and patients with postoperative adverse events such as rebleeding or a postoperative RD from visual acuity analysis, the BCVA appeared to be slightly lower than expected. This may be explained by the fact that patients with satisfying surgical results and uncomplicated conditions often visit established ophthalmologist for postoperative examinations. Therefore, unfortunately, the number of patients included into postoperative visual acuity analysis was relatively small and the visual acuity may not have been entirely representative due to the matters mentioned above, which must be taken into consideration when interpreting the results.

Preoperative visual acuity was better in the delayed vitrectomy group (1.84 logMAR) compared to the early vitrectomy group (2.17 logMAR). This suggests that the initial conservative approach in patients who underwent delayed

vitrectomy resulted in only a partial clearance of hemorrhage with the need of vitrectomy to restore vision to the greatest possible extent.

Equal to a comparison between early and delayed vitrectomy in eyes with vitreous hemorrhage caused by PDR[75] our study also showed no significant difference in the final visual acuity between the two groups (early: 0.79 logMAR; delayed: 1.03 logMAR). Fassbender et al[75] suggested that an early intervention decreases the need for repeated office visits and the time patients spend with low vision.

Therefore, it would be interesting to know how many patients, depending on the cause of vitreous hemorrhage, need vitrectomy in the long term and if any factors, additional to the cause, exist that help estimate the need for vitrectomy. Further studies answering these questions would help vitreoretinal surgeons to know in which cases, additional to RD, ocular trauma or operative complications, an early surgical intervention is reasonable due to a justified assumption of a missing self-clearance of vitreous hemorrhage.

4 CONCLUSION

In summary, this study showed that the most common causes for vitrectomy-requiring vitreous hemorrhage in non-diabetic patients are RVOs, PVDs and retinal tears with or without RD. Vitrectomy was performed at an average of 65.1 ± 65.7 days after initial presentation with vitreous hemorrhage. 46.2% of the eyes included in this study underwent surgery within the first 30 days. The visual outcome of this group was equal to the visual outcome of the delayed vitrectomy group. Hence, further studies investigating predictive factors for non-clearing vitreous hemorrhage would be beneficial, as an early intervention in case of a predictable missing of self-clearance would decrease the time patients have to spend with low vision.

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