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Major review

Misdirected aqueous flow in rhegmatogenous retinal detachment: A pathophysiology update

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ARTICLE INFO

Article history:
Received 1 December 2013
Received in revised form
20 July 2014
Accepted 23 July 2014
Available online 10 August 2014

Keywords:
rhegmatogenous retinal detachment
aqueous misdirection
retinal tear
posterior vitreous detachment
vitreoretinal traction
pathophysiology

ABSTRACT

It is widely accepted that the origin of subretinal fluid in rhegmatogenous retinal detachment (RRD) is liquid vitreous and that posterior vitreous detachment (PVD) and associated retinal tears are caused by vitreoretinal traction from intra-ocular currents, contraction of collagen fibers, and gravity. These explanations, however, are incomplete. We present a new synthesis of experimental and clinical evidence, updating understanding of fundamental pathophysiological processes in RRD. Misdirected aqueous flow is shown to more convincingly explain the origin of subretinal fluid in clinical RRD, to be the most likely cause of acute PVD and retinal tear formation, and also to contribute to initial detachment of the retina at retinal tears. Misdirected aqueous flow in RRD is a pathophysiological process, rather than the "aqueous misdirection syndrome", and occurs without visible anterior chamber shallowing or acute glaucoma.

1. Introduction

Rhegmatogenous retinal detachment (RRD) is characterized by fluid passing from the vitreous through one or more full-thickness retinal breaks into the subretinal space between the retina and the retinal pigment epithelium (RPE).[27,53,74,93] We present a new synthesis of experimental and clinical evidence to update understanding of fundamental pathophysiological processes in RRD:

1.1. The source of subretinal fluid (SRF) in RRD is generally characterized as "liquefied vitreous",[24,62,82] although Quintin and Brassueur suggested it comes from serum, vitreous, and retina.[74] The vitreous, however, cannot by itself be the source of continuous flow of subretinal fluid in clinical RRD as it has a finite volume and no cells capable of fluid secretion.

1.2. Acute posterior vitreous detachment (PVD) is widely accepted to be caused by contraction of vitreous collagen fibers[16,19,76] and intraocular liquid vitreous currents[1,16,19,26,40,58,76] exacerbated by gravity,[62] or by spontaneous emptying of the central vitreous fluid into the subhyaloid space, with collapse, sinking, and forward movement of remaining formed vitreous gel.[38,87]

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0039-6257/$ – see front matter
http://dx.doi.org/10.1016/j.survophthal.2014.07.002

Spontaneous collapse and redistribution of liquid vitreous do not, however, explain a sudden, forceful, fluid flux in acute PVD, and experimental evidence shows that vitreous liquefaction alone is not sufficient to cause acute PVD.[60,62] Intraocular currents in liquefied vitreous resulting from eye movements,[16,40,58] combined with degenerative weakening of vitreous cortex-ILM adhesion,[62,84,87] degenerative shortening of vitreous fibers,[76,84] and tears in the vitreous cortex[60] do not adequately explain forceful fluid movement in acute PVD. The vitreous normally contains no tissue capable of acute, forceful contraction, so it is unlikely that contraction within or of the vitreous body is sufficient to cause acute PVD and its complications such as a Weiss ring or retinal tears.

1.3. Retinal tears also are generally believed to be caused by contraction of vitreous collagen fibers[16,19,76] and vitreous currents.[1,16,19,26,40,58,76] In the absence of direct eye or head trauma, however, intravitreal currents from ocular saccades are not likely to generate sufficient force to tear the retina[76] and should produce tears hinged posteriorly as well as anteriorly and most frequently in the horizontal meridians in cultures whose reading saccades are horizontal; neither is the case. We present experimental and clinical evidence for misdirected flow of aqueous humor into the vitreous as playing four important roles in RRD pathophysiology:
   1) the source of subretinal fluid
   2) the most likely cause of acute PVD
   3) the usual cause of retinal tears
   4) probably contributing to initial retinal separation from the RPE at a retinal break

We also present possible mechanisms for misdirected aqueous flow in RRD.

2. Misdirected aqueous flow in RRD is not the "aqueous misdirection syndrome"

It is important to distinguish misdirected aqueous flow in RRD, a pathophysiological process, from the "aqueous misdirection syndrome", also known as "malignant glaucoma", an unusual form of angle closure occurring infrequently as a complication of glaucoma surgery and rarely after other eye surgery or in the absence of surgery.[29,80,89]

In the aqueous misdirection syndrome, for reasons that are still controversial,[73] aqueous secretion by the ciliary body is believed to flow entirely posteriorly through the anterior vitreous face into the vitreous, misdirected by a valve effect of vitreous gel and/or ciliary processes.[15,17,29,80,89,90,104] Misdirected aqueous is trapped and accumulates in the vitreous, causing vitreous expansion, pushing the lens–iris diaphragm and ciliary processes forward, shallowing the anterior chamber, and closing the angle.

In RRD, as we will demonstrate, "misdirected" aqueous flow into the vitreous occurs, but is distinctly different from the aqueous misdirection syndrome. The posterior flow of aqueous is partial and has not been observed to provoke anterior chamber shallowing nor angle closure.

3. Does misdirected aqueous, posterior flow of aqueous into the vitreous, exist in RRD?

Aqueous is in intimate contact with the anterior vitreous face, and there is continuous, efficient exchange of small molecules between the aqueous and vitreous by diffusion,[46,50,52,57,65,102] but there is little or no flow of fluid between them when the anterior vitreous face is intact.[46,50,52,57,65,97,102,105] In clinical RRD, however, there is compelling evidence that SRF is largely aqueous humor that flows posteriorly through the vitreous to pass via retinal breaks into the subretinal space, as suggested by Pederson.[70,71]

3.1. *Experimental evidence*

3.1.1. *Ascorbate in SRF*

Elevated ascorbate levels present in RRD subretinal fluid most probably originate from aqueous humor.[101]

3.1.2. *Tracer studies*

Experiments involving vitreous clearance of tracers in RRD strongly support posterior fluid flow through the vitreous into the subretinal space.[9,69,70,98] In particular, fluorescein-labeled isothiocyanate-dextran injected in the vitreous of monkey eyes with RRD passed into subretinal space at 1.12 μL/min, and it was suggested that liquid vitreous flowing into the subretinal space was removed by the RPE and then "replaced by posterior chamber aqueous humor, creating a misdirected flow of aqueous."[70]

3.2. *Clinical evidence*

3.2.1. *The RPE pump*

The RPE continuously pumps SRF into the choroid in RRD,[54,70,74,99] an estimated 261 $\mu L/cm^2/day$[11] —13.6 cm^2 of RPE can drain 3.5 mL/day into the choroid.[74] In a clinical RRD, SRF removed by the choroid must be replaced by a continuous flow of fluid through the retinal breaks, although a continuous supply of fluid flow cannot come from a finite volume of degenerated liquid vitreous. There is no convincing evidence of a significant source of fluid production other than aqueous humor.

3.2.2. *Relative hypotony in RRD*

Eyes with RRD usually have an intraocular pressure lower than in the normal contralateral eye. This is explained by partial posterior flow of aqueous through the vitreous, across the retinal breaks into subretinal space, and finally across the RPE into the choroid[10,24,30,53,69–71,101] rather than by decreased aqueous production, as once believed.[69] Hypotony is not always present in RRD because some eyes have pre-existent abnormally low coefficients of aqueous outflow and some have clogging of the trabecular meshwork by inflammatory cells from low grade anterior uveitis or by photoreceptor disks—the Schwartz syndrome.[39,55,56,67] In the Schwartz syndrome, photoreceptor disks pass from the subretinal space into and anteriorly through the vitreous and the anterior vitreous face into the posterior chamber and then into the anterior chamber (confirming a defect in the vitreous face).