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Does The *Bursa Pre-Macularis* Protect the Fovea from Shear Stress? A Possible Mechanical Role.

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Short Title: Does the Pre-Macular Bursa Protect the Fovea?

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Highlights

- The Pre-Macular *Bursa* (PMB) is a pocket of liquid within the vitreous gel structure and is placed anterior to the macula
- The presence of the PMB significantly reduces Wall Shear Stress (WSS) at the macular surface during saccadic motion by reducing friction
- Shear Stress related gene expression has been largely reported
- Shear stress modifications secondary to PMB disappearance with aging may trigger age-related disease

Abstract

Purpose of present study is to evaluate if the Pre-Macular Bursa (PMB) modifies Wall Shear Stress (WSS) at the retinal surface during saccadic movements. We created a 25,000 cells mathematical in order to calculate WSS throughout the retinal surface. The posterior pole was divided into 3 zones comprising 400 nodes each. Zone 1 (radius 3.5mm; 0°-17°) corresponding to the PMB area; zone 2 (concentric annular area 5 mm in radius; 22°) and zone 3 (concentric annular area 5.5 mm; 28°). The saccade covered 50° in 0.17s. Recording time was 0.34 s. The PMB reduced WSS significantly at the macula and increased it in the immediate surroundings. Average WSS in zone 1 was 1.53 ± 1.01 (max 4.23 Pa) with PMB Vs 6.94 ± 9.23 (max 35.83 Pa) without; in zone 2 was 9.39 ± 10.33 (max 48.36 Pa) with PMB Vs 6.95 ± 9.40 (max 38.60 Pa) without while in zone 3 was 8.41 ± 10.03 (max 43.16 Pa) with PMB Vs 6.88 ± 9.42 (max 39.43 Pa) without. $p<0.001$ in all cases. The PMB significantly reduces WSS over the retinal surface underlying the bursa region; conversely, WSS slightly increases it in the immediate neighboring areas.

Key Words: Pre-macular Bursa; Bursa Premacularis; Finite Element Modeling; Vitreous Fluidics; Retinal detachment

Introduction

The Pre-Macular *Bursa* (PMB) or *Bursa Pre-Macularis* or Posterior Pre-Cortical Vitreous Pocket (fig. 1; movie 1) is a small reservoir of liquid vitreous placed anteriorly to the fovea and consistently present in virtually all eyes, at least in the first decades of life (Spaide 2014). The PMB is connected to the Area of Martegiani in about 50% of eyes and a further space named "*supramacular bursa*" can also be detected in more than 80% of cases.

Several strategies have been deployed to unravel the details of vitreous structure: Eisner (1975) Jongebloed (1987) and Worst (1995) mostly used dissection techniques while more recently, Optical Coherence Tomography (OCT) helped clarify the complex anatomy of liquid canals crossing the vitreous (Kishi 1990, Itakura 2015, Shimada 2011 and Schaal 2014).

While our knowledge of the elusive labyrinth of pockets and canals improved, their function remains enigmatic. Ontogenetic theories hypothesize they represent remnants of the foetal primary vitreous while Worst (1995) postulated they act as biochemical ways of communication between the anterior chamber and the retina. More recently, Spaide (2014) proposed a mechanical role for the PMB based on OCT observation, hypothesizing an energy damping mechanism.

Present paper introduces a mathematical model aimed at calculating retinal surface Wall Shear Stress (WSS) during saccadic movements, in the presence or absence of the Pre-Macular Bursa. Purpose of the paper is to understanding whether the presence of a liquid volume within the gel matrix anterior to the fovea dissipates mechanic energy reducing shear stress.

Materials and Methods

Vitreous and Retinal Surface Mesh Construction

We used Computational Fluid Dynamics methods to evaluate the dynamics of the vitreous and assess the shear stress on the retinal surface. We solved numerically motion equations of a viscoelastic fluid: namely, the momentum balance and the conservation of mass, in case of unsteady laminar flow, by means of the Finite Volume Method and applying a dynamic mesh technique. The governing equations were solved using the open source library OpenFOAM, previously validated in a vast spectrum of engineering applications (Garau 2017, Badas 2017; Isakova 2017).

The eye was modelled as a sphere (24 mm in diameter), with a spherical cap on the anterior side mimicking the indentation of the lens (Figure 2) (Abouali 2012; Modareszadeh 2014). The adopted mesh is an H-O structured grid with 25,000 cells, built with a central cube and other six blocks, which was chosen to limit the numerical error due to the non-orthogonality of the computational grid. The vitreous chamber was filled with a viscoelastic gel-like fluid reproducing the vitreous and simulations ran under two conditions: the first condition, used as a reference, did not include the PMB. The second condition modeled the PMB as a spheroidal layer of fluid, 550 μm thick and 7000 μm in diameter, separating the vitreous body from the retina.

No-slip conditions were imposed at the wall. In the presence of PMB, due to its limited thickness, we assumed a laminar Couette flow and postulated a linear law of transmission of the shear stress through the depth of the bursa:

$$WSS = \mu\, VV / D$$

where μ is the viscosity of the Newtonian fluid filling the PMB ($\mu = 10^{-3}$ Pa s), VV is the vitreous velocity and D is the thickness of the bursa.

The vitreous viscoelastic behaviour was described through the Oldroyd-B model (with relaxation time $\lambda = 0.097$ s and elastic modulus $G = 10.31$ Pa) describing the linear behaviour of a viscoelastic fluid (Oldroid 1950).

Saccadic Motion

To evaluate the consequence of ocular saccadic motion to the vitreous chamber, a rotation of amplitude A = 50° was imposed to the eye, with a duration D = 0.1375 s, attaining peak angular velocities of $\Omega_p = 546.67°/s$ at time Tp = 0.0344 s (Figure 3;

Gellman 1991). The saccade moved horizontally and the saccadic wave function was built using a polynomial function (Repetto 2005):

$$\theta(t) = c_0 + c_1 t + c_2 t^2 + c_3 t^3 + c_4 t^4 + c_5 t^5$$

where t represents the time, θ the angular displacement, and the c coefficients are reported in Table 1. After the maximum rotation, A = 50°, was achieved, the simulation was prolonged for a time D (i.e. the saccade duration, D = 0.1375 s) in order to observe the flow evolution during the deceleration of the vitreous following the saccadic motion.

Main Outcome Measures

Mean and maximum Wall Shear Stress (WSS) at the retina in the presence or absence of the Pre-Macular Bursa were calculated throughout the mesh surface for the duration of the entire saccade (see movie 2). Data related to 62 discrete point located along the horizontal section through the fovea (fig.2) were analysed and ANOVA performed. In order to study PMB effects on the foveal, juxta-foveal, peri-foveal and extrafoveal area, WSS statistical analysis also included three concentric regions centred in the foveola comprising 400 points each. Zone comprised a circular area of 3.5 mm in radius while Zones 2 and 3 comprised concentric circular rings up to 4.5 and 5.5 mm, respectively. p values less than 0.05 have been considered statistically significant.

Results

Figures 4a reports mean Wall Shear Stress through the saccade at points located along the horizontal section through the fovea (as shown in fig. 2), while Figure 4b reports WSS net difference with and without the PMB.

Wall Shear Stress of the five centre-most locations is significantly lower in presence of the PMB and significantly higher immediately adjacent to it ($p<0.001$ for all points marked with an asterisk in fig. 4a and 4b). Interestingly, the increase of WSS determined by the PMB is asymmetrically skewed towards the side of rotation, spanning 5 points (roughly 15°) rotation-wise (fig. 4, points 317 through 328) and only one point (about 5°) counter-rotation wise (fig. 4, point 22). All other points distributed along the transverse (horizontal) section through the macula highlighted in fig.2 did not any show difference.

Mean and maximum WSS as a function of distance from the foveola is rendered as colour map in fig. 5, where zones 1, 2 and 3 as above defined, have also been overlaid. The presence of the PMB determined highly significant difference in maximum WSS (compare fig. 5a to 5c) and mean WSS throughout all three Zones (compare fig. 5b to 5d), as also reported in tables 2 and 3. It should also be noted that in the presence of the PMB, Zone 1 had the lowest mean and maximum WSS compared to Zone 2 and 3, and Zone 1 without PMB (table 2).

Wall Shear Stress behaviour throughout saccade time span is plot in figure 6 for the three Zones as mean WSS ± standard deviation and has also been rendered in 3D (movie 2). The presence of PMB significantly lowered WSS in the region underlying the bursa while it slightly increased in the adjacent concentric zones 2 and 3 (see also fig. 5).

Discussion

The Pre-Macular Bursa is a pocket of liquid vitreous located anterior to the macula. Originally described as a space of optical transparency overlying the fovea by Eisner (1975), Worst (1995) defined its boundaries through ink injection but it was not investigated into details until Kishi used anatomic specimens (Kishi 1990) and OCT (Li 2014). The PMB changes shape with posturing (Itakura 2013), increases volume with age and height with myopic refraction (Li 2014), and may change shape, become virtual almost disappearing or simply move more anteriorly after complete Posterior Vitreous Detachment (PVD) occurs.

The PMB physiologic function remains largely unknown. Worst (1995) hypothesized that the system of liquid canals within the gel matrix acted as preferential ways of communication for ions, cells and molecules traveling from the anterior to the vitreous chamber and the macula while more recently Spaide (2004) proposed a mechanical role purely based on merely anatomic observations through Swept Source OCT imaging.

The eyeball is exposed to exceptional mechanical stress due to the high angular velocity and acceleration of saccades; the eyes perform 2-3 saccades per second during wake and maintain intense motion through sleep, with over 100,000 saccades a day. On the other hand, the necessity to generate still images is imperative to survival and is therefore likely that evolution selected and privileged structures capable of damping energy.

We developed a mathematical model to test the hypothesis that the presence of a pool of liquid in front of the fovea decreases saccade-induced Wall Shear Stress exerted by vitreous motion on the underlying retinal surface. Previous studies calculated WSS of different degrees of tamponade fill (Angunwela 2011, David 1998) and scleral geometry (Meskauskas 2012) but did not pay particular attention to the PMB itself.

Indeed our data demonstrate that PMB reduces significantly WSS at the macula (fig. 4 and 5 and 7) while increasing it more peripherally (table 2; Zones 2 and 3; fig. 5), especially on the side of rotation (fig. 5 and 8).

The physical explanation resides in the high acceleration transmitted to the visco-elastic content of the vitreous chamber by the extrinsic muscles through the sclera: the resulting laminar flow exerts friction on the retinal surface as a function of vitreous velocity and viscosity. The presence of liquid vitreous compartmentalized over the macula, allows the vitreous gel to slip over the liquid pocket (the PMB) which, in turn, exerts very little friction over the macula (see also movie 2). The reduction of friction in the region of the *bursa* is partially compensated for by a certain increase of the WSS in the surrounding region and, in particular, in the region opposite to the direction of motion (fig. 6, x = -6mm) during the deceleration phase.

Our results indicate that the PMB consistently reduces both maximum and mean WSS (fig. 6) throughout the saccade: the average WSS in the absence of the PMB is 4.5 times higher while maximum WSS was is 8.75 times higher (table 2), suggesting a protective role on the fovea.

The 3D rendering better clarifies WSS behaviour and localization (fig. 7, 8 and movie 3, 4, 5 and 6): as the saccade begins, the vitreous motion lags a fraction of a second and then accelerates, generating shear stress over the retinal surface. At the end of the acceleration phase, WSS increases in the neighbourhood of the bursa, in the direction of rotation (fig. 7B).

As soon as the eye motion stops, the opposite happens and the vitreous decelerates due to the friction with the still retinal surface until kinetic energy dissipates completely. During this phase, the region of increased WSS is located adjacent to the macula opposite to rotation direction. This second phase lasts longer compared to the accelerating phase and leaves an apparent mark on the mean WSS map plotted in fig. 6D (movies 4, 5 and 6). A saccade in the opposite direction would obviously produce a specular increase of WSS on the other side of the *bursa*.

Wall Shear Stress time behaviour in the three zones at increasing distance from the fovea (table 2 and 3) shows how much the presence of the PMB influences vitreous motion throughout the vitreous chamber during the saccade (fig. 6, movies 4 and 5).

For the principle of energy conservation, overall vitreous inertia remains the same, regardless to PMB presence; therefore the reduced friction corresponding to the *bursa* region has to be compensated elsewhere in its vicinity, in order for the retinal surface to accelerate (in the first phase of the saccade) and then decelerate (after the saccade) the vitreous body.

This is apparent in fig. 6 where Zone 1 shows a much lower WSS in the presence of the bursa (fig. 6A) while concentric areas (Zones 2 and 3; fig. 6b and C, respectively) show a significantly higher WSS and a greater variability in time.

The present study suffers the typical pitfalls of mathematical models applied to biology and biomechanics in general. The vitreous intrinsic microscopic anatomy determines its anisotropy and there is unpredictable retinal adhesion at the vitreous base, vessels, fovea and optic nerve that may significantly influence vitreous motion. Moreover, the mechanical properties of biologic tissues remain matter of controversy despite the use of reverse engineering techniques to mitigate uncertainties.

Although all named factors may interfere with the quantitative aspect of the study, the proof of principle holds that the presence of a liquid reservoir (the PMB) adjacent to the wall of a rotating hollow sphere filled with gel (the vitreous chamber) causes a significant decrease in WSS over the surface “protected” by the fluid pocket itself.

The term “protective” implies a beneficial effect that seems intuitive but needs further scrutiny and validation. We know with certainty that many cell types including neurons (Liu 2013), vascular endothelial cells, muscle cells (Juffer 2014), connective cells (Chou 2016) and many others, respond to shear stress expressing a whole set of genes that modulate neuroprotection, angiogenesis and inflammation, according to flow characteristics (laminar vs turbulent) intensity and time variability (Wragg 2014).

Interestingly enough, all the above cellular mechanisms participate to the pathogenesis of several degenerative diseases affecting the retinal area underlying the PMB, including many maculopaties and particularly age-related macular degeneration, whose progression (Jackson 2013) and prognosis (Schramm 2014) have been clearly associated to vitreous adhesion conditions (Jackson 2013).

As life expectance increases and vitreous changes affects virtually the entire aging population, there is little doubt that we are witnessing the consequences of WSS changes over the retinal surface. Muller cells (Lindquist 2010; Davis 2012) and retinal ganglion cells modulate gene expression in response to shear stress (Rennier 2015) and even the extracellular matrix components adjust to shear stress (Chou 2016). On the other hand, the prevalence of macular pathology including vitreo-retinal interface syndromes and age-related macular degeneration is certainly increasing although improved diagnostic and higher index of suspicion improved detection rate.

Does WSS play a role in such pathologies? It most likely does. Can we discriminate its specific pathogenic role from other aging mechanism and treat it? We certainly cannot.

We believe a deeper understanding of fascinating and still mysterious vitreous fluid dynamics, almost neglected so far, will help shed more light on many vitreo-retinal diseases and answer such questions.

Conclusions

The presence of the PMB significantly reduces WSS at the macula and increases it immediately outside the area covered by the PMB, a mechanism that might retain protective significance for the most delicate part of the retina. Considering saccadic eye motion exposes the retinal surface to extreme shear stress second only to endothelial cells of great arterial vessels, and the growing evidence of shear stress-related gene expression in cell types also present in the retina, further studies on the issue seem justified if not warranted.

Figure 1 – OCT scan of the Pre-Macular Bursa (PMB). The PMB is centred on the fovea. Note the presence of a similar pocket of fluid anterior to the optic nerve known as the Martegiani Area from which the Cloquet's Canal stems. (see also movie 1).

Figure 2 – Horizontal section of 3D mesh; 0° corresponds to the foveola and blue dots represent the 62 points considered along the horizontal section, spaced 5°- 6°. In red is reported a schematic drawing of the bursa and the blue arrow indicates saccade direction.

Figure 3 – Saccade characteristics: A) Angle span as a function of time and B) Angular velocity as a function of time (Angular Acceleration).

Figure 4 – **A)** Average Wall Shear Stress of the 62 horizontal section points highlighted in fig. 2, calculated in the presence of Pre-Macular Bursa (PMB; black columns) and without the PMB (grey columns). The red bar overlying distinct points adjacent to 0° represents the extension of the PMB and spans 5 tested locations. The asterisk denotes a significant difference ($p<0.01$ in all cases, both in A and B). The blue arrow indicates saccade direction **B**) Difference of Mean Wall Shear Stress (WSS) with the Pre-Macular Bursa (PMB) – WSS without the PMB. Note that WSS delta is negative underneath the Bursa and positive right outside it as Mean WSS is much less within the area of the PMB and significantly higher outside the PMB. Also note that WSS delta is skewed in the saccade direction.

Figure 5 – Colour map of Maximum (A and B) and Average (C and D) Wall Shear Stress (WSS) within a 10x16 mm rectangle centred on the foveola. A) shows a uniformly distributed Max WSS without the Pre-Macular Bursa (PMB); B) Max WSS in the presence of the bursa is much lower underneath the PMB. C) Average WSS in the absence of the PMB and D) in the presence of the PMB; note the red spot to the left hand side of the blue area representing the bursa region and in the direction of the saccade (see text).

Figure 6 – Wall Shear Stress (WSS) of Zones 1, 2 and 3 (see also table 2 and 3) during the saccade: A) Zone 1 with (red lines) and without the Pre-Macular Bursa (PMB; blue lines); B) Zone 2 with (red lines) and without (blue lines) the PMB; C) Zone 3 with (red lines) and without blue lines) the PMB. In order to represent all points located within the same Zone, continuous lines represent the mean curve and dashed lines the mean ± 2 standard deviations. Note that Zone 1 WSS remains extremely low throughout the duration of the saccade in the presence of PMB while varies considerably elsewhere.

Figure 7 – 3D Finite Element Modelling frame at 0.028 seconds. A) The model with no Pre-Macular Bursa (PMB) shows a uniform distribution of Wall Shear Stress (WSS) across the posterior pole while B) the model with PMB clearly demonstrates an area of reduced WSS corresponding to the bursa itself (see also movie 3, 4 and 5).

Figure 8 – 3D Finite Element Modelling frame at 0.057 seconds. A) The model with no Pre-Macular Bursa (PMB) shows a steady reduction compared to fig. 6 and uniform distribution Wall Shear Stress (WSS) across the posterior pole. B) The model with PMB also shows WSS reduction throughout the posterior pole with the notable exception of an area to the right hand side of the fovea in the sense of rotation where WSS is increased (see also movie 3, 4 and 6). Note that this area (seen from the outside) corresponds to the red spot to the left hand side of the bursa area (seen from inside) and in the sense of the rotation.

List of Supplemental digital content:

Movie 1: movie 1 oct.mov

Movie 2: movie 2 surgical image Bursa premaculare 1 video.mp4

Movie 3: movie 3 3D rendering with Vs without.avi

Movie 4: movie 4 rot_singola_WssCube_with bursa.mp4

Movie 5: movie 5 rot_singola_WssCube_without bursa.mp4

Movie 6: movie 6 3D section WSS with Vs wihout bursa.mp4

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