Biomechanical Predictors of Rhegmatogenous Retinal Detachment in Myopic Patients

Preditores Biomecânicos de Descolamento de Retina em Doentes com Alta Miopia

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ABSTRACT

INTRODUCTION: The prevalence of myopia is expected to increase significantly in the following decades. Moreover, axial myopia is associated with rhegmatogenous retinal detachment (RRD), a major cause of visual impairment in these patients. RRD develops after the dynamic interaction between the vitreous and the retina. Axial length (AL) is a well-described risk factor, but alone is insufficient to predict RRD. The main aim of this study was to analyze, dynamically and *in vivo*, ocular biomechanics in high myopic patients with RRD. Our secondary outcome was to address demographic, biometric and biomechanical predictors of RRD.

METHODS: Observational cross-sectional case-control study, set in the Surgical Retina Clinic, Ophthalmology Department, Centro Hospitalar e Universitário do Porto, Portugal, that included subjects with myopia and history of RRD in one eye (RRD group), together with a control group of age and AL-matched subjects with no history of retinal tear or RRD in any eye. In the RRD group, only the fellow non-RRD non-operated eye was included for analysis. Biomechanical assessment was performed with Corvis Scheimpflung Technology® (Oculus, Germany) and AL was measured with Anterion® (Heidelberg, Germany).

RESULTS: This study included for analysis 34 subjects (17 eyes of 17 patients in each group). Age (p=0.959), AL (p=0.879) and intraocular pressure (p=0.489) were well matched between groups. A multivariable logistic regression confirmed an independent effect of A1 Deflection Amplitude (standardized coefficient = -1.096, Wald test p-value=0.027), HC time (-1.207, p=0.030), and height (1.554, p=0.030) on RRD, with an area under the curve in the ROC analysis for this model of 0.897. We found no association between biometric or biomechanical parameters and the characteristics of RRD or final best-corrected visual acuity.

CONCLUSION: To our knowledge, this is the first study evaluating *in vivo* ocular biomechanics in the development of RRD. We observed that the eyes of patients with RRD have stiffer measured biomechanics when compared to controls. The different biomechanical behavior be-

tween the vitreous and the sclera (to which the retina is ultimately attached) results in higher shear stress at the vitreoretinal interface. We hypothesize that RRD develops in cases where this balance is disrupted by a stiff sclera on one side and a compact vitreous on the other. The association between body height and RRD may also relate to systemic genetically determined biomechanics.

KEYWORDS: Biomechanical Phenomena; Myopia; Retinal Detachment; Treatment Outcome; Vitreous Body.

RESUMO

INTRODUÇÃO: É expectável que a prevalência da miopia aumente nas próximas décadas. Além disso, a miopia axial está associada a descolamento de retina (DR), uma causa importante de défice visual nesses doentes. O DR desenvolve-se a partir da interação dinâmica entre o vítreo e a retina. O comprimento axial (CA) é um fator de risco bem descrito, mas isoladamente é insuficiente para prever o DR. O objetivo principal desde estudo foi analisar, dinamicamente e *in vivo*, a biomecânica ocular em doentes com miopia e DR.

MÉTODOS: Estudo transversal caso-controlo, na secção de Retina Cirúrgica do Serviço de Oftalmologia do Centro Hospitalar Universitário do Porto, que incluiu participantes com AM e antecedentes DR em um dos olhos (grupo DR), juntamente com um grupo de controlo com participantes com idade e CA emparelhados, mas sem antecedentes de rasgadura de retina ou DR em nenhum dos olhos. No grupo DR, apenas o olho adelfo (sem antecedentes de DR ou cirúrgica intraocular) foi incluído para a análise. A analise da biomecânica ocular foi realizada com Corvis Scheimpflung Technology® (Oculus, Germany) e AL foi medido com o Anterion® (Heidelberg, Germany).

RESULTADOS: O estudo incluiu para análise 34 participantes (17 olhos de 17 participantes em cada grupo). A idade (p=0,959), o CA (p=0,879) e a pressão intraocular (p=0,489) não foram diferentes e estavam bem emparelhados entre os grupos. Uma análise de regressão logística multivariável confirmou o efeito independente da amplitude de deflexão A1 (coeficiente padronizado = -1,096, p-value do teste de Wald = 0,027), tempo HC (-1,207, p=0,030) e altura corporal (1,554, p=0,030) no DR, com área sob a curva da análise ROC deste modelo de 0,897. Não foram encontradas associações entre parâmetros biométricos ou biomecânicos e as características do DR (localização, severidade, presença de paliçadas) ou com a melhor acuidade visual corrigida final.

CONCLUSÃO: Este é o primeiro estudo a avaliar *in vivo* a biomecânica ocular na fisiopatologia do DR. Observámos que os olhos de doentes com DR apresentaram medições biomecânicas tendencialmente mais rígidas quando comparados com o grupo de controlo. O diferente comportamento entre o vítreo e a esclerótica (à qual a retina se liga em última instância) resulta numa tensão de cisalhamento ao nível da interface vítreo-retiniana. O DR desenvolve-se em casos em que este balanço é quebrado pela esclerótica rígida de um lado e o humor vítreo compacto do outro. A associação entre a altura corporal e o DR pode também estar associada à biomecânica.

PALAVRAS-CHAVE: Corpo Vítreo; Descolamento de Retina; Fenómenos Biomecânicos; Miopia; Resultado do Tratamento.

INTRODUCTION

Myopia is a common and complex ophthalmological entity and was estimated to affect approximately 2.5 billion people worldwide in 2020.[1] As it is increasing, myopia is expected to be present in about 50% of the world's population in 2050 and high myopia (associated with a refractive error of at least −6.00D or an axial length over 26 mm) in almost 10%.[2,3]

The pathological changes resulting from myopia, namely high myopia, are already one of the main causes of severe visual impairment, even blindness, particularly in East Asian countries, like China,[4] Singapore,[5] or Japan,[6] but also in Europe[7,8] and in the United States,[9] frequently in active young patients. Therefore, it carries a huge personal, social, and economic burden in the working-age population and should be addressed as an emerging global health problem.

Myopia is a well-known risk factor for rhegmatogenous retinal detachment (RRD), and it is an even stronger risk factor in young people, as described in a large series of our

center.[10] The risk increases with an increasing myopia, and it was reported to be up to 10 times higher for myopia larger than -3.00D.[11]

The discussion about the factors associated with the increased risk of RRD in myopic eyes was centered on static anatomical factors for many years. Despite this, the vitreous is a mobile structure. In 2015 a group showed, based on a quantitative mathematical model, that the vitreous humor and the retina are exposed to a significantly higher shear stress during physiologic eye rotations in myopic compared to emmetropic eyes and that this is not only due to higher axial lengths but with different widths and eye shapes, leading to disintegration of the collagen network, an increased risk of vitreous liquefaction, PVD and ultimately RRD.[11-14]

One of the current paradigm shifts in medicine is the evolution from static to dynamic examinations. Despite the critical role played by the vitreous humor in the internal dynamics of the posterior segment of the eye,[15] only few studies have tried to characterize its viscoelastic properties.

In vivo characterization of ocular biomechanics is currently possible with the Corvis Scheimpflug Technology® (Oculus, Germany) which is a non-contact tonometer with a coupled ultra-high-speed Scheimpflug camera that records at 4330 frames/second an 8 mm horizontal corneal cross-section during corneal deformation after an external force is applied through a collimated air-puff.[16-18] This device had been extensively validated to detect risk of cornea ectasia in corneal refractive surgery, but its potential goes further. Our group started to study the dynamic properties of the vitreous with this technology and we hypothesized that the vitreous could play a centripetal force on the globe.[19]

The main aim of this study was to analyze, *in vivo*, ocular biomechanics in high myopic patients with RRD. Our secondary purpose was to address demographic, ocular and systemic biometric and biomechanical predictors of RRD.

METHODS

DESIGN

Single-center observational cross-sectional case-control study. The study adhered to the tenets of the Declaration of Helsinki. Approval was obtained from the 'Departamento de Ensino, Formação e Investigação' (DEFI), nr: 130-DEFI-132-CE. The informed consent from the patients was waived due to total anonymization and confidentiality of the data and the absence of detailed individual data.

SETTING

Surgical Retina Clinic, Ophthalmology Department, Centro Hospitalar e Universitário do Porto, Portugal.

POPULATION

Case group (RRD group): individuals above 18 years-old with myopia (over -3.00D of myopia in manifest refraction spherical equivalent) and history of RRD in one eye only.

Control group: age and axial length-matched subjects with no history of retinal tear or RRD in any eye, recruited from routine appointments in the general ophthalmology clinic.

EXCLUSION CRITERIA

Exclusion criteria were history of bilateral RRD; previous intraocular surgery (other than unilateral vitrectomy in the case group), previous buckle surgery; previous corneal ablative procedures, presence of corneal dystrophies or other corneal or scleral diseases; pterygium or other conjunctival conditions; inability to fixate; phthisis bulbi or other ocular decompensated status; cognitive inability to perform the exams.

CLINICAL DATA

Information from clinical records and the last complete ophthalmological examination was analyzed, including age, gender, manifest refraction spherical equivalent (MRSE).

OCULARB IOMECHANICAL AND BIOMETRIC DATA

Biomechanical assessment was performed with Corvis Scheimpflung Technology® (Oculus, Germany). Only exams with 'OK' quality score were included. Parameters from the three major timepoints were recorded: time from the initiation of air puff until the first applanation (A1), second applanation (A2) and highest concavity (HC). Additional first-generation parameters from the maximum deformation on the oscillatory phase (Max) and from Whole Eye Movement (WEM) were analyzed. The complex second-generation parameters included the Corvis Biomechanical Index (CBI), Stiffness Parameter in A1 (SP-A1) and Stress Strain Index (SSI). AL was measured with the swept-source optical coherence biometer Anterion® (Heidelberg, Germany).

STATISTICAL ANALYSIS

As the treatment for RRD (namely pars plana vitrectomy) may change ocular biomechanics, only the fellow eye of patients with unilateral RRD (the eye with no history of RRD or previous surgery) composed the case group. In the control group, only one eye was included for analysis, chosen to match the number of right/left eyes in the case group.

Nonparametric tests were used for direct comparisons and correlations. A logistic regression was performed to assess the effect of multiple variables in subjects with RRD. All values are shown as mean ± standard deviation unless otherwise specified. All p-values (p) were 2-sided, and p-values < 0.05 were considered significant.

ETHICAL CONSIDERATIONS

This study was performed accordingly to the principles of the Declaration of Helsinki. Moreover, all exams

performed are considered non-invasive. Approval was obtained from the 'Departamento de Ensino, Formação e Investigação', with the number 130-DEFI-132-CE. The informed consent from the patients was waived due to total anonymization and confidentiality of the data and the absence of detailed individual data.

RESULTS

This study included for analysis 34 subjects (17 eyes of 17 patients in each group). The women-to-men ratio was 9/8 in the RRD group and 10/7 in the control group.

Demographic, clinical and biometric data of the total sample is described in Table 1. A comparison between groups regarding demographic, clinical, biometric, and biomechanical data is shown in Table 2.

A multivariable logistic regression confirmed the independent effect of A1 Deflection Amplitude (standardized coefficient = -1.096, Wald test *p*-value=0.027), HC time (-1.207, *p*=0.030), and body height (1.554, *p*=0.030) on RRD with an area under the curve in the ROC analysis for this model of 0.897. Conditional estimates plots for each of the variables in the logistic regression model are shown in Fig. 1.

Characterization of the RRD is detailed in Table 3. Mean final BCVA was 0.29 (standard deviation 0.30, minimum 0.01, maximum 1.00). We found no association between biometric or biomechanical parameters and the characteristics of RRD or final BCVA.

DISCUSSION

To our knowledge, this is the first study to evaluate in vivo ocular biomechanics in the development of retinal detachment. We observed that the eyes of patients with retinal detachment have different measured biomechanics compared to controls with no history of retinal detachment and matched age and axial length. The direction of our results seems to relate to stiffer corneal biomechanics in eyes with RRD, independently of axial length. Although the latest generation biomechanical index (SSI), that control for IOP and corneal thickness, did not reach statistical significance, it was higher in the RRD group, meaning a stiffer behavior. The reasons for these findings are not fully understood as the research on the role of biomechanics in RRD is scarce.

A previous study by our group has suggested the role of the vitreous in ocular biomechanics.[17] It was the first study to analyze vitreous biomechanics using Corvis ST®. Whole eye movement (WEM) was the measurement that best correlated with the effect of the vitreous. The reduction of WEM after surgical removal of the vitreous suggested that is exerts an anterior-posterior traction on the globe. However, we observed no significant changes in WEM in the current study,

The different biomechanical behavior between the vitreous and the sclera (to which the retina is ultimately attached) results in traction at the vitreoretinal interface. We hypothesize that RRD develops in cases where this balance is disrupted by a stiff sclera on one side and a compact vitreous on the other. This study did not measure scleral biomechanics directly. Still, both cornea and sclera have similar molecular structure (despite a different supramolecular organization) that is genetically determined.[18] Moreover, scleral biomechanics seem to directly affect the cornea deformation induced by Corvis ST.[19]

There are two factors that occur universally and enhance this traction: 1) the vitreous matrix contraction and volume reduction that occur with age and 2) physiological ocular movements, namely saccades, that lead to the highest shear stress between the retina and the vitreous.[20] Again, this occurs because of the different mechanical properties of both tissues. The contribution of ocular biomechanical may explain why some patients develop RRD while others do not, despite all being subject to vitreous contraction and ocular movements.

We note that other mechanisms, also related to biomechanics, are implicated in myopic eyes. The retina in high myopic eyes is fundamentally different from emmetropic eyes: it is thinner and thus more prone to tears.[21] Additionally, the oval shape of globe promotes higher shear stress on the retina than in a comparable sphere with the same volume.[22]

Furthermore, Pickett-Seltner *et al* evaluated the molecular composition of the vitreous in chicken myopes. They found it to be similar to those with normal eyes,[23] highlighting the importance of the dynamical and biomechanical component, instead of a biochemical one, in developing RRD.

Anomalies of the peripheral vitreoretinal interface, like lattice degeneration have been associated with an increased risk of retinal tears and RD.[24,25] It is however unclear if those anomalies are a cause of RRD or if they are a consequence of a common pathological process. We found no different biomechanics in eyes with lattice degeneration.

Table 1. Demographic and clinical data of the full sample.

	Median	Interquartile Range	Minimum	Maximum
Age [years]	38.490	7.386	19.000	59.000
Height [m]	1.650	0.157	1.570	1.870
Weight [kg]	69.000	24.500	52.000	93.000
Body Mass Index	24.609	4.816	20.313	34.160
Axial lengh [mm]	27.630	4.370	23.060	32.000
Pachy [µm]	544.000	42.000	485.000	654.000
IOP [mmHg]	14.000	3.000	9.500	24.000

standard deviation (SD); intraocular pressure (IOP).

Table 2. Comparison between rhegmatogenous retinal detachment group and control group regarding demographic, clinical, biometric, and biomechanical data.

Variable	RDD		Control			
	Median	IQR	Median	IQR	Mann-Whitney statistics	*p*-value
Age [years]	38.000	7.000	38.981	6.230	146.500	0.959
Height [m]	1.710	0.130	1.600	0.020	189.000	**0.020**
Weight [kg]	78.000	19.000	63.000	12.000	181.500	**0.043**
Body Mass Index	24.676	5.253	24.609	4.026	150.000	0.405
Axial lengh [mm]	28.175	5.870	27.000	3.200	109.000	0.879
Pachy [µm]	532.000	49.000	555.000	32.000	108.000	0.218
IOP [mmHg]	14.500	2.500	14.000	3.000	165.000	0.489
Def. Amp. Max [mm]	1.124	0.132	1.102	0.119	156.000	0.705
A1 Time [ms]	7.713	0.262	7.621	0.303	175.000	0.306
A1 Velocity [m/s]	0.146	0.017	0.152	0.018	127.000	0.558
A2 Time [ms]	22.138	0.426	22.234	0.560	136.000	0.786
A2 Velocity [m/s]	-0.296	0.046	-0.285	0.037	150.000	0.863
HC Time [ms]	16.863	0.462	17.556	0.231	56.500	**0.002**
Peak Dist, [mm]	5.252	0.350	5.154	0.250	152.500	0.796
Radius [mm]	6.334	1.079	6.274	0.647	154.000	0.760
A1 Deformation Amp, [mm]	0.136	0.013	0.135	0.009	142.500	0.959
HC Deformation Amp, [mm]	1.124	0.132	1.102	0.119	156.000	0.705
A2 Deformation Amp, [mm]	0.321	0.077	0.312	0.079	140.000	0.890
A1 Deflection Length [mm]	2.258	0.128	2.287	0.128	114.500	0.449
HC Deflection Length [mm]	6.783	0.613	6.869	0.408	141.000	0.919
A2 Deflection Length [mm]	2.644	1.285	2.608	1.043	167.000	0.454
A1 Deflection Amp, [mm]	0.088	0.006	0.092	0.007	87.500	**0.051**
HC Deflection Amp, [mm]	0.992	0.154	0.969	0.143	164.000	0.513
A2 Deflection Amp, [mm]	0.100	0.013	0.106	0.014	124.000	0.490
Deflection Amp, Max [mm]	0.992	0.122	1.000	0.126	166.000	0.469
Deflection Amp, Max [ms]	16.675	0.885	16.348	0.771	161.000	0.582
Whole Eye Movement Max [mm]	0.232	0.074	0.219	0.062	140.000	0.890
Whole Eye Movement Max [ms]	21.976	0.914	21.601	1.054	187.000	0.150
A1 Deflection Area [mm²]	0.167	0.034	0.166	0.022	144.500	1.000
HC Deflection Area [mm²]	3.627	0.727	3.569	0.640	161.000	0.586
A2 Deflection Area [mm²]	0.231	0.045	0.233	0.069	168.000	0.428
A1 dArc Length [mm]	-0.016	0.003	-0.018	0.003	200.500	**0.053**
HC dArc Length [mm]	-0.122	0.032	-0.126	0.031	161.500	0.569
A2 dArc Length [mm]	-0.020	0.007	-0.021	0.006	164.000	0.510
dArcLengthMax [mm]	-0.138	0.033	-0.156	0.042	163.000	0.535
Max InverseRadius [mm^-1]	0.189	0.020	0.199	0.033	109.500	0.234
DA Ratio Max (2mm)	4.112	0.415	4.178	0.468	121.000	0.433
PachySlope [µm]	33.758	5.939	37.089	10.703	113.000	0.290
DA Ratio Max (1mm)	1.532	0.078	1.547	0.049	136.000	0.786
ARTh	587.881	162.693	717.181	263.626	118.000	0.375
Integrated Radius [mm^-1]	9.084	1.211	9.915	1.579	116.000	0.339
SP A1	107.252	20.226	106.989	29.479	137.000	0.986
CBI	0.170	0.243	0.100	0.287	112.500	1.000
SSI	0.823	0.234	0.812	0.180	147.000	0.491

trhegmatogenous retinal detachment (RD); interquartile range (IQR); intraocular pressure (IOP); first applanation (A1); second applanation (A2); highest concavity (HC)

Genetic factors are involved in RRD. Familial history is a risk factor for RRD independently of myopia.[26] The two primary genes recently associated with RRD in adults are FAT3 and COL22A1.[27] The latter codes a newly described gene product, collagen XXII, present only at tissue junctions.[28] To this date, expression of COL22A1 has not been studied in the eye but it would be interesting to evaluate its role in ocular biomechanics and RRD.

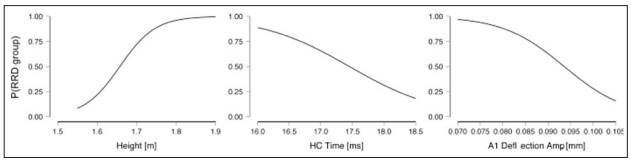

Figure 1. Conditional estimates plots and 95% confidence intervals for each variable (height, HC time and A1 deflection amplitude) in a multivariable logistic regression model predicting rhegmatogenous retinal detachment in the fellow eye.

probability (P); rhegmatogenous retinal detachment (RRD); highest concavity (HC); first applanation (A1).

Table 3. Characterization of the rhegmatogenous retinal detachments.

	Frequency (relative frequency)
Presence of horseshoe retinal tear (vs retinal hole)	8 (47%)
Superior location of the rhegmatogenous lesion (vs inferior)	5 (29%)
Endocular tamponade with silicon oil (vs gas)	2 (12%)
Presence of peripheral lattice degeneration	5 (29%)

We observed an association between body height and RRD. Particularly, subjects in the RRD group were taller. We also observed a difference in weight but the fact that BMI was not different between groups, highlights height as the leading player in our findings. So far, no study has associated height with the risk of RRD. In fact, 80% of height variation is under genetic control.[29] A large meta-analysis of genome-wide association studies concluded that height-associated genes are involved in skeletal, cartilage, and connective tissue development.[30]

Interestingly, some systemic genetic disorders that affect connective tissue, such as Marfan syndrome, have been associated with an increased risk of RRD.[31] Patients with Marfan syndrome are taller than the general population and have differences in the biomechanics of both extraocular tissues (namely arteries) and ocular tissues.[32,33] A previous study using the Ocular Response Analyzer (ORA) has shown that Marfan patients have increased corneal deformation, decreased bending resistance, and reduced energy dissipation capacity.[34] Additionally, a genotype-phenotype correlation has been described between the different *FBN1* mutations in Marfan syndrome and several ocular phenotypes (presence of ectopia lentis or posterior staphyloma) and biometric determinants (axial length, corneal thickness, and corneal diameter).[35] In Marfan syndrome, mutated fibrillin acts by activating transforming growth factor β (TGFβ), leading to its clinical manifestations.[36] Interestingly, TGFβ is also involved in scleral remodeling in experimental myopia.[37]

Most of the research performed on scleral biomechanics focused on the pathophysiology of glaucoma.[38] Axial length is a well-described risk factor, but alone is insufficient to predict RRD.[39] Still, we believe that the relation between scleral and vitreous biomechanics together with height deserves further research.

Out study group included the fellow non-RRD eye of patients with RRD. This design avoids the bias of analyzing biomechanics in eyes that were previously vitrectomized. In fact, our previous work confirmed the changes that occur after vitrectomy.[17] Additionally, unpublished data of our group observed that eyes with acutely detached retina (before the surgical intervention) also show changes in biomechanics measurements, probably due to hypotony or due to the release of vitreous traction.

This study has some limitations. The small sample underpowers the study and it impairs finding differences between groups. It would be interesting to see if a larger sample would reach statistical significance in WEM and SSI. Additionally, if we had a larger model, together with a validation set, it would be possible to create a risk score considering biometric and biomechanical variables. Another limitation of this study is its cross-sectional design. It is unknown if the subjects in the control group will develop RRD with time. A longitudinal study with high myopic patients would therefore be appropriate to find a true association with RRD. To overcome this limitation, we assembled a control group with age and axial length perfectly matched eyes.

CONCLUSION

Retinal detachment is expected to become an even largen burden worldwide. Current scientific knowledge is insufficient to predict the risk of RRD.[39]

We observed that the eyes of patients with RRD have stiffer measured biomechanics when compared to controls. The different biomechanical behavior between the vitreous and the sclera (to which the retina is ultimately attached) results in higher shear stress at the vitreoretinal interface. We hypothesize that RRD develops in cases where this balance is disrupted by a stiff sclera on one side and a compact vitreous on the other.

The association between body height and RRD may also relate to systemic genetically determined biomechanics. Investigation considering biomechanics is warranted and dynamic analysis of the eye may give a contribution. For the future, strategies for prevention or prophylaxis of RRD may be the right direction.

CONTRIBUTORSHIP STATEMENT / DECLARAÇÃO DE CONTRIBUIÇÃO:

JHM, PMB: Study design, data collection, statistical analysis and interpretation, article writing and approval of the final version.

AM, PS, SP: Data collection, statistical analysis and interpretation.

AM, RA, PM, JMB: Study design, methods supervision, critical review of the manuscript and approval of the final version.

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