# The Role of Corneal Biomechanics as a Predictor of Choroidal Neovascular Membranes in Myopic Eyes

# O Papel da Biomecânica Corneana como Preditor de Membranas Neovasculares Coroideias em Olhos Míopes

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## ABSTRACT

**INTRODUCTION:** Myopic maculopathy in the form of choroidal neovascularization (mCNV) may display a significant impact in visual function, frequently in active young patients. The present work was aimed to describe corneal biomechanics in myopic eyes with history of mCNV treated with intravitreal anti-vascular endothelial growth factor (VEGF) and compare it with the fellow eyes. Secondary purposes were to make subgroup analysis within the group of mCNV eyes and to address predictors of disease and treatment response

**METHODS:** Single center observational cross-sectional case-control study including individuals above 18 years old with myopia and history of mCNV treated with intravitreal anti-VEGF in one eye in Centro Hospitalar e Universitário do Porto. Data from clinical records was taken regarding treatment-related information. A questionnaire including personal demographic, biometric and lifestyle related data was performed. Biomechanical assessment was made by means of Scheimpflug camera, through Corvis ST® (OCULUS). Ocular biometric parameters were addressed by Anterion® (Heidelberg). Data from Macular anatomical assessments were performed through the OCT platform Spectralis® (Heidelberg).

**RESULTS:** Sixty four eyes from 32 patients were included, 87.5% females, with a mean age of 62.5+-13.3 years old. A tendency to lower HC-time was found in eyes with mCNV. Eyes with macular bruch membrane holes (MBMH) showed higher WEM Max time and TBI and belonged to individuals with more physical activity and more UV-light exposure. Several biomechanical parameters correlated with lifestyle habits. Membrane diameter was moderate-to-strongly correlated with softer biomechanical behavior, while number of intravitreal anti-VEGF injections associated without a consistent pattern. A pure biomechanical model was built to predict the presence of MBMH, including the WEM Max time and the TBI, with an AUROC of 0.808 and with no influence from AL or intraocular pressure.

**CONCLUSION:** To the authors knowledge, this is the first study evaluating in vivo ocular biomechanics in mCNV. Biomechanics showed promising results as a predictor of mCNV, more specifically of MBMH. It seems to be associated with lifestyle factors and future studies should be

performed to confirm our findings, paving the way to the introduction of a dynamic paradigm in mCNV risk assessment of myopic eyes.

**KEYWORDS:** Biomechanical Phenomena; Bruch Membrane; Choroidal Neovascularization; Cornea; Myopia; Vascular Endothelial Growth Factor.

## RESUMO

**INTRODUÇÃO:** A maculopatia miópica na forma de neovascularização coroideia (mCNV) pode apresentar um impacto significativo na função visual, frequentemente em pacientes jovens ativos. O presente trabalho teve como objetivo descrever a biomecânica corneana em olhos míopes com histórico de mCNV tratados com anti-fator de crescimento endotelial vascular (VEGF) intravítreo e compará-la com os olhos contralaterais. Os objetivos secundários foram analisar subgrupos dentro do grupo de olhos com mCNV e abordar preditores de doença e resposta ao tratamento.

**MÉTODOS:** Estudo observacional unicêntrico, transversal, caso-controlo, incluindo indivíduos acima de 18 anos com miopia e história de mCNV unilateral tratada com anti-VEGF intravítreo, no Centro Hospitalar e Universitário do Porto. As informações relacionadas com o tratamento foram adquiridas através dos processos clínicos dos pacientes. Foi realizado um questionário incluindo dados pessoais demográficos, biométricos e relacionados ao estilo de vida. A avaliação biomecânica obteve-se através da tecnologia de câmara de Scheimpflug, por meio do Corvis ST® (OCULUS). Os parâmetros biométricos oculares foram adquiridos pelo biómetro Anterion® (Heidelberg). As avaliações anatómicas maculares foram realizadas por meio da plataforma OCT Spectralis® (Heidelberg).

**RESULTADOS:** Foram incluídos 64 olhos de 32 pacientes, 87,5% do sexo feminino, com média de idade de 62,5+-13,3 anos. Foi encontrada uma tendência para um menor HC-time em olhos com mCNV. Olhos com buracos na membrana de Bruch macular (MBMH) apresentaram valores mais elevados de WEM time max e TBI e pertenciam a indivíduos com mais atividade física e maior exposição à luz UV. Vários parâmetros biomecânicos correlacionaram-se com os hábitos de vida. O diâmetro da membrana foi moderada a fortemente correlacionado com um comportamento biomecânico menos rígido, enquanto o número de injeções de anti-VEGF intravítreo se associou sem um padrão consistente. Um modelo biomecânico puro foi construído para prever a presença de MBMH, incluindo o WEM time max e TBI, com AUROC de 0,808 e sem influência de AL ou da pressão ocular.

**CONCLUSÃO:** Segundo conhecimento dos autores, este é o primeiro estudo avaliando a biomecânica ocular in vivo em olhos com mCNV. A biomecânica mostrou resultados promissores como preditor de mCNV, mais especificamente de MBMH. Parece estar associado a fatores de estilo de vida e estudos futuros devem ser realizados para confirmar nossos achados, abrindo caminho para a introdução de um paradigma dinâmico na avaliação de risco de mCNV de olhos míopes.

**PALAVRAS-CHAVE:** Cornea; Fator de Crescimento do Endotélio Vascular; Fenómenos Biomecânicos; Lâmina Basilar da Corioide; Miopia; Neovascularização de Coroide.

## 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.

High myopia (HM) is associated with a refractive error of at least −6D and/or an axial length ≥ 26 mm and is estimated to affect almost 10% of the world´s population in 2050.[2] The pathological changes resulting from HM are already one of the main causes of serious visual impairment, even blindness, particularly in East Asian countries, like China[3], Singapore[4] or Japan,[5] but also in Europe[6,7] and United States.[8] Myopic maculopathy (MM) may display a significant impact in visual function, frequently in active young patients. Therefore, is an emerging global health burden that urgently needs to be addressed.

One of the most serious complications of myopia is myopic choroidal neovascularization (mCNV), which often

leads to a sudden onset but progressive decline in central vision and is associated with a poor prognosis unless treated. Furthermore, 35% of patients with mCNV develop bilateral disease in the fellow eye within 8 years.[9] Although intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapies have had a major impact on the management of patients with mCNV, there remain significant gaps in our understanding of this condition and how to best manage it.

The advent and improvement of optic coherence tomography (OCT) technology lead to a comprehensive classification of MM.[1] The current paradigm stands that lacquer cracks (LC) and macular bruch membrane holes (MBMH) are the most common predisposing factors for the development of mCNV.[1,9,10] However, this involves an anatomic static view, much related with axial length (AL), lacking a more dynamic view, including ocular biomechanical status and lifestyle factors.

In vivo characterization of ocular biomechanics can be made nowadays with the Corvis ST® (Corvis, OCULUS, Wetzlar, Germany) which is a non-contact tonometer with a coupled ultra-high-speed Scheimpflug camera that records the deformation process at 4330 frames/second along an 8 mm horizontal corneal cross-section during corneal deformation.[11-13] The Scheimpflug-camera-derived basic analysis describes corneal biomechanical behavior in three major timepoints: applanation 1 (A1), Highest concavity (HC) and applanation 2 (A2). Additionally, it gives information from the maximum deformation on the oscillatory phase (MaxDT) and from whole eye movement (WEM), all within the nearly 35 milliseconds interval in which the cornea makes the ingoing and outgoing movements after the air puff.[14] Table 1 describes Scheimpflug camera-derived corneal biomechanical parameters with explanation and abbreviations.

The present work was aimed to describe corneal biomechanics in myopic eyes with history of mCNV treated with intravitreal anti-VEGF and compare it with the fellow eyes without history of mCNV. Secondary purposes were to make subgroup analysis within the group of mCNV eyes and to address predictors - biometric, biomechanical, demographic and lifestyle – of disease and treatment response.

# MATERIAL AND METHODS

## DESIGN

This is a single-center observational cross-sectional case-control study.

## 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 'Centro Hospitalar e Universitário do Porto Ethical Commission', with the number 158-DEFI/160-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

Medical Retina Clinic at Centro Hospitalar e Universitário do Porto.

## POPULATION

Individuals above 18 years old with myopia (phakic spherical equivalent less than -1.00 Diopter) and history of mCNV treated with intravitreal anti-VEGF in one eye in a *Pro-Re-Nata* regimen. The case group was composed by the eye with a mCNV which underwent intravitreal anti-VEGF treatment. The control group was composed by the fellow eye of the same patient.

## INCLUSION AND EXCLUSION CRITERIA

Myopic patients with more than one year history of mCNV in one eye and no history of mCNV in the fellow eye were included. Exclusion criteria were: any ocular surgery other than cataract surgery; cataract surgery less than 1 year before; presence of corneal dystrophies or other corneal and scleral diseases; pterygium or other conjunctival diseases; inability to fixation; phthisis bulbi or other ocular decompensated status; cognitive inability to perform exams or answer the questionnaire

## CLINICAL DATA GATHERING

Data from clinical records was taken regarding treatment-related information: number and timing of treatments and used drugs.

## OCULAR BIOMECHANICAL ASSESSMENT

Biomechanical assessment was made by means of Scheimpflug camera, with Corvis ST® (OCULUS), through the dynamic corneal response (DCR) parameters. Only exams with 'OK' quality score were included. Both Corvis-derived-IOP (cIOP) and parameters from the three major timepoints were recorded: time from the initiation of air puff until the first applanation (A1T), highest concavity (HCT) and second applanation (A2T). Additional 1st generation parameters from the maximum deformation on the oscillatory phase (Max) and from whole eye movement (WEM) along with the biomechanically-corrected-IOP (bIOP) and the composed 2nd generation parameters including Corvis Biomechanical Index (CBI), Tomographic and Biomechanical Index (TBI), Stiffness Parameter in A1 (SP-A1) and Stress Strain Index (SS-I) were analyzed. Pachymetry assessment was made through the Corvis-derived central corneal thickness (cCCT). All Scheimpflug-based parameters used in the study and its explanation are summarized in Table 1.

## OCULAR BIOMETRIC ASSESSMENT

Ocular biometric parameters were addressed by the biometer Anterion® (Heidelberg). Data from axial length (AL), central corneal thickness (CCT) and white-to-white (W-T-W) was collected.

**Table 1.** **Scheimpflug camera-derived corneal biomechanical parameters with explanation.**

| Parameters | Abbreviation | Explanation |
|---|---|---|
| cIOP [mmHg] | cIOP | Corvis-derived intraocular pressure |
| cCCT [μm] | cCCT | Corvis-derivated central corneal thickness |
| **1st generation parameters** | | **Description** |
| Deformation Amp. Max [mm] | MaxDefoA | Corneal deformation amplitude during MaxDT, as the sum of corneal deflection amplitude and MaxWEM |
| A1 Time [ms] | A1T | Time from the measurement beginning to the first applanation moment |
| A1 Velocity [m/s] | A1V | Velocity of the corneal apex during the first applanation |
| A2 Time [ms] | A2T | Time from the measurement beginning to the second applanation moment |
| A2 Velocity [m/s] | A2V | Velocity of the corneal apex during the second applanation |
| HC Time [ms] | HCT | Time from the measurement beginning to the moment of reaching the highest concavity (HC) |
| Peak Dist. [mm] | HCPD | Distance between the corneal peaks at the HC |
| Radius [mm] | HCR | Radius of corneal curvature during the HC |
| A1 Deformation Amp. [mm] | A1DefoA | Corneal deformation amplitude during A1, as the sum of corneal deflection amplitude and MaxWEM |
| HC Deformation Amp. [mm] | HCDefoA | Corneal deformation amplitude during HC, as the sum of corneal deflection amplitude and MaxWEM |
| A2 Deformation Amp. [mm] | A2DefoA | Corneal deformation amplitude during A2, as the sum of corneal deflection amplitude and MaxWEM |
| A1 Deflection Length [mm] | A1DL | Horizontal length of the flattened cornea at the A1 |
| HC Deflection Length [mm] | HCDL | Horizontal length of the flattened cornea at the HC |
| A2 Deflection Length [mm] | A2DL | Horizontal length of the flattened cornea at the A2 |
| A1 Deflection Amp. [mm] | A1DA | Corneal deflection amplitude during A1, determined as the displacement of the corneal apex in relation to the initial state without the MaxWEM quantification |
| HC Deflection Amp. [mm] | HCDA | Corneal deflection amplitude during HC, determined as the displacement of the corneal apex in relation to the initial state without the MaxWEM quantification |
| A2 Deflection Amp. [mm] | A2DA | Corneal deflection amplitude during A2, determined as the displacement of the corneal apex in relation to the initial state without the MaxWEM quantification |
| Deflection Amp. Max [mm] | MaxDA | Corneal deflection amplitude during MaxDT |
| Deflection Amp. Max [ms] | MaxDT | Moment of the maximum corneal deflection, during the oscillatory phase near HC |
| Whole Eye Movement Max [mm] | MaxWEM | Amplitude of the Maximum whole eye movement |
| Whole Eye Movement Max [ms] | MaxWEMT | Time at which occurs the amplitude of the Maximum whole eye movement (near A2) |
| A1 Deflection Area [mm²] | A1DArea | Deflection area in A1 |
| HC Deflection Area [mm²] | HCDArea | Deflection area in HC |
| A2 Deflection Area [mm²] | A2DArea | Deflection area in A2 |
| A1 dArc Length [mm] | A1dArcL | Delta arc length of corneal surface in A1 |
| HC dArc Length [mm] | HCdArcL | Delta arc length of corneal surface in HC |
| A2 dArc Length [mm] | A2dArcL | Delta arc length of corneal surface in A2 |
| dArcLengthMax [mm] | MaxdArcL | Delta arc length of corneal surface in MaxDT |
| **2nd generation parameters** | | **Description** |
| Max InverseRadius [mm^-1] | MIR | 1 / HCR |
| DA Ratio Max (2mm) | DARM2 | Ápex MaxDA / MaxDA at 2 mm from the ápex |
| PachySlope [μm] | PqS | Peripheric (8 mm horizontal) pachymetry / Ápex pachymetry |
| DA Ratio Max (1mm) | DARM1 | Ápex MaxDA / MaxDA at 1mm from the ápex |
| Ambrosio Relational Thickness (8 mm) | ARTh | Ambrosio Relational Thickness within the horizontal 8 mm cornea of the image |
| Biomechanically-corrected IOP | bIOP | IOP adjusted for biomechanical parameters |
| Integrated Radius [mm^-1] | IR | Area under the curve of the 1/HCR function |
| Stiffness parameter in A1 | SP-A1 | Air puff pressure - bIOP / A1DA |
| Corvis biomechanical index | CBI | Exponential function score made through a logistic regression analysis of 6 parameters (SP-A1, DARM1, DARM2, ARTh, A1V and MaxDefoA) and adjusted for IOP and CCT to describe ectasia risk |
| Stress Strain Index | SS-I | Finite element modeling algorithm for the estimation of the non-linear in vivo biomechanical behaviour in corneal with normal topography |

## ANATOMICAL ASSESSMENT

Macular assessments were performed through the OCT platform Spectralis® (Heidelberg). A thorough posterior pole evaluation was made. The *posterior pole protocol* encompassed 61 horizontal cuts within a square of horizontal 30º and vertical 25º, including optic disc and macula, with *EDI-enhancement*. Data was collected from mCNV diameter, the number and localization of the mCNV - foveal/perifoveal membranes (FM) were defined as those within de 500 µm area from de fovea -, and the presence of MBMH - defined as areas with absence of the choriocapillaris, Bruch's membrane, RPE and photoreceptors.

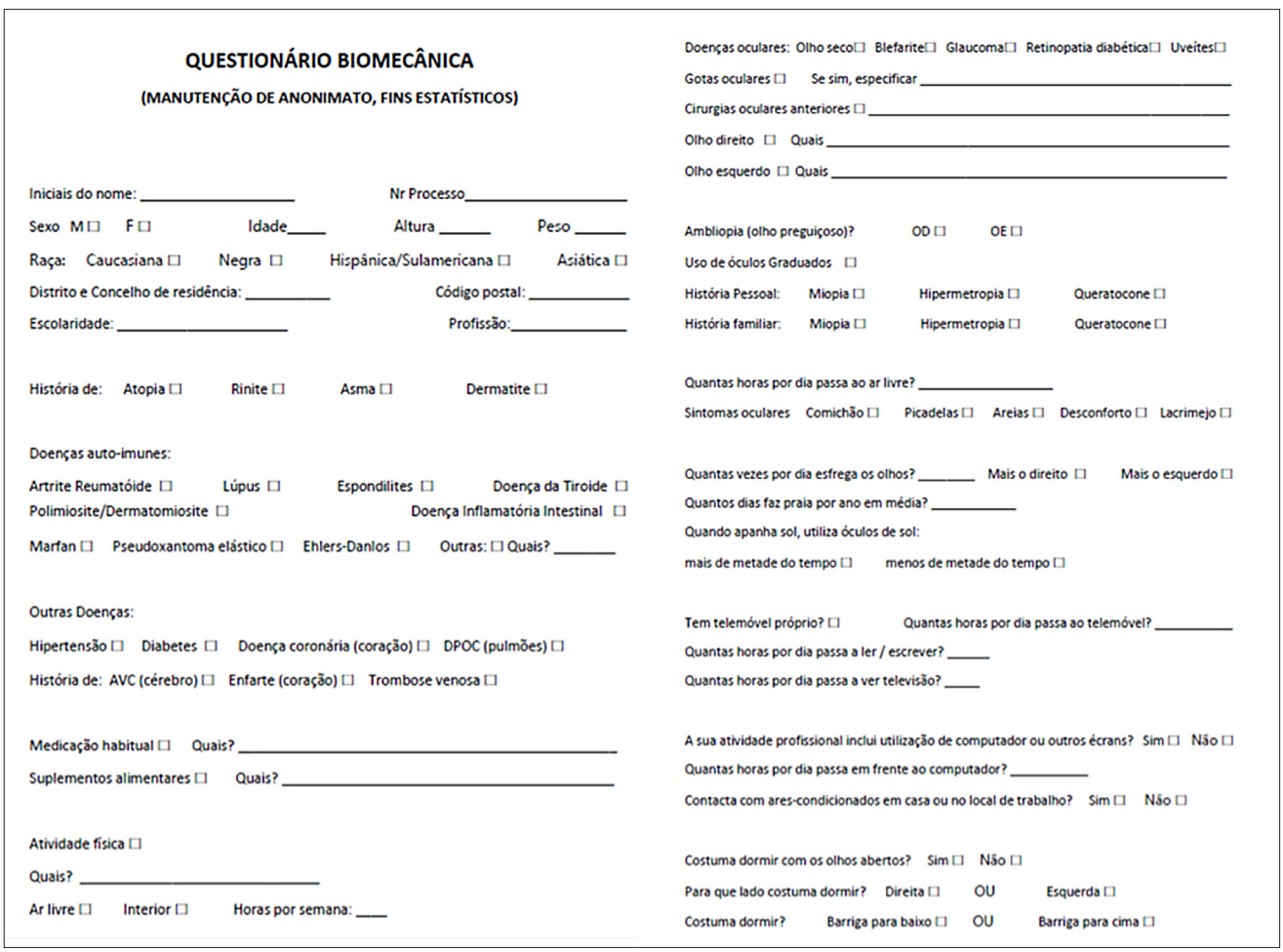
## DEMOGRAPHIC AND LIFESTYLE ASSESSMENT

A questionnaire (Attachment 1) accepted and validated by the Centro Hospitalar e Universitário do Porto Ethical Commission (nr 158-DEFI/160-CE), including personal demographic, biometric and lifestyle related data was performed.

## STATISTICAL ANALYSIS

Descriptive statistics of all dataset were calculated for demographic, clinical, biometric, anatomic corneal biomechanical and treatment-related parameters. Comparisons were made between groups. Normality of the data was tested with the Shapiro-Wilk and Kolmogorov-Smirnov tests. When parametric analysis could be applied, the Student t-test was used to compare the variables. When nonparametric tests were needed, the Wilcoxon rank-sum test was applied. The $\chi 2$ was used to compare nominal and ordinal variables. The nonparametric Spearman's rank correlation coefficient was used within mCNV eyes group to address the relationships between biomechanical, biometric, demographic, lifestyle and treatment-related parameters.

A logistic regression was performed to assess the effect of corneal biomechanics in mCNV eyes. Candidate predictors with $p<0.25$ were included in a multivariable stepwise elimination analysis in which $p<0.05$ served as the criterion for retention into the full model. Receiver operating characteristic (ROC) analyses were performed to determine the area under the ROC curve (AUROC) for that model. The previous methodology was applied in the group of mCNV eyes to find a model capable of predicting the presence of MBMH.



**QUESTIONÁRIO BIOMECÂNICA**

**(MANUTENÇÃO DE ANONIMATO, FINS ESTATÍSTICOS)**

Iniciais do nome: _____ Nr Processo_____

Sexo M☐ F☐ Idade____ Altura _____ Peso _____

Raça: Caucasiana☐ Negra ☐ Hispânica/Sulamericana☐ Asiática ☐

Distrito e Concelho de residência: _____ Código postal: _____

Escolaridade: _____ Profissão:_____

História de: Atopia ☐ Rinite ☐ Asma ☐ Dermatite ☐

Doenças auto-imunes:

Artrite Reumatóide ☐ Lúpus ☐ Espondilites ☐ Doença da Tiroide ☐

Polimiosite/Dermatomiosite ☐ Doença Inflamatória Intestinal ☐

Marfan ☐ Pseudoxantoma elástico ☐ Ehlers-Danlos ☐ Outras: ☐ Quais? _____

Outras Doenças:

Hipertensão ☐ Diabetes ☐ Doença coronária (coração) ☐ DPOC (pulmões) ☐

História de: AVC (cérebro) ☐ Enfarte (coração) ☐ Trombose venosa ☐

Medicação habitual ☐ Quais? _____

Suplementos alimentares ☐ Quais? _____

Atividade física ☐

Quais? _____

Ar livre ☐ Interior ☐ Horas por semana: ____

Doenças oculares: Olho seco☐ Blefarite☐ Glaucoma☐ Retinopatia diabética☐ Uveítes☐

Gotas oculares ☐ Se sim, especificar _____

Cirurgias oculares anteriores ☐ _____

Olho direito ☐ Quais _____

Olho esquerdo ☐ Quais _____

Ambliopia (olho preguiçoso)? OD ☐ OE ☐

Uso de óculos Graduados ☐

História Pessoal: Miopia ☐ Hipermetropia ☐ Queratocone ☐

História familiar: Miopia ☐ Hipermetropia ☐ Queratocone ☐

Quantas horas por dia passa ao ar livre? _____

Sintomas oculares Comichão ☐ Picadelas ☐ Areias ☐ Desconforto ☐ Lacrimejo ☐

Quantas vezes por dia esfrega os olhos? _____ Mais o direito ☐ Mais o esquerdo ☐

Quantos dias faz praia por ano em média? _____

Quando apanha sol, utiliza óculos de sol:

mais de metade do tempo ☐ menos de metade do tempo ☐

Tem telemóvel próprio? ☐ Quantas horas por dia passa ao telemóvel? _____

Quantas horas por dia passa a ler / escrever? _____

Quantas horas por dia passa a ver televisão? _____

A sua atividade profissional inclui utilização de computador ou outros écrans? Sim ☐ Não ☐

Quantas horas por dia passa em frente ao computador? _____

Contacta com ares-condicionados em casa ou no local de trabalho? Sim ☐ Não ☐

Costuma dormir com os olhos abertos? Sim ☐ Não ☐

Para que lado costuma dormir? Direita ☐ OU Esquerda ☐

Costuma dormir? Barriga para baixo ☐ OU Barriga para cima ☐

Attachment 1. Questionnaire

**Table 2.** Descriptive statistics from demographic, biometric, lifestyle, tomographic and treatment-related data

| DEMOGRAPHICS AND BIOMETRICS | Mean | SD |
|---|---|---|
| Age (years) | 62.5 | 13.3 |
| High (cm) | 161.0 | 7.4 |
| Weigth (kg) | 65.7 | 11.6 |
| | % | |
| Feminine sex (%) | 87.5 | |
| Alergic diseases (%) | 6.7 | |
| Autoimune diseases (%) | 16.7 | |
| Pseudophakic (%) | 50.0 | |
| Eye rubbing (%) | 42.9 | |
| **LIFESTYLE** | **Mean** | **SD** |
| Hours per week of physical activity (hours) | 2.0 | 2.5 |
| Open air hours per day (hours) | 2.8 | 1.8 |
| Annual beach days (days) | 9.7 | 19.7 |
| Daily cellphone hours (hours) | 1.4 | 1.5 |
| Daily reading hours (hours) | 0.8 | 2.1 |
| Daily TV hours (hours) | 1.8 | 1.8 |
| Daily PC hours (hours) | 1.0 | 2.1 |
| Eye rubbing (times per day) | 2.7 | 3.0 |
| | % | |
| Sleeping laterality - right (%) | 46.9 | |
| Sleeping laterality - left (%) | 34.4 | |
| Sleeping position - ventral (%) | 12.5 | |
| Sleeping position - dorsal (%) | 40.6 | |
| Physical activity (%) | 50.0 | |
| Outdoor physical activity (%) | 47.5 | |
| Sun glasses less than half of time (%) | 43.8 | |
| **NEOVASCULAR MEMBRANES - mCNV eyes** | **Mean** | **SD** |
| Membrane diameter (μm) | 1168.5 | 689.5 |
| | % | |
| Foveal/parafoveal membrane (%) | 59.4 | |
| Out of fovea membrane (%) | 40.6 | |
| Various membranes (%) | 6.3 | |
| Macular Bruch membran holes (%) | 46.9 | |
| **TREATMENT - mCNV eyes** | **Mean** | **SD** |
| Number of intravitreal anti-VEGF injections (n) | 8.03 | 7.11 |
| Treatment length (months) | 28.5 | 36.1 |

All analysis were performed using the SPSS v26.0 and JASP software's. 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.

## RESULTS

The present study included 64 eyes from 32 patients, four men and 28 women, with a mean age of 62.5±13.3 years old. Demographic, clinic and lifestyle related data taken from the questionnaire are described in Table 2.

Treated eyes had a mean of 8.03±7.11 intravitreal injections during 28.5±36.1 months in average. Mean membrane diameter was of 1168.5±689.5 μm and 47% had MBMH.

**Table 3.** Ocular biometrics and corneal biomechanical data

| OCULAR BIOMETRICS | Mean | SD |
|---|---|---|
| Axial Length (mm) | 24.42 | 2.50 |
| CCT (μm) | 550.87 | 42.85 |
| W-T-W (mm) | 11.67 | 0.45 |
| **CORNEAL BIOMECHANICS** | **Mean** | **SD** |
| cIOP [mmHg] | 15.959 | 3.241 |
| Pachy [μm] | 553.197 | 42.975 |
| Def, Amp, Max [mm] | 1.132 | 0.133 |
| A1 Time [ms] | 7.886 | 0.392 |
| A1 Velocity [m/s] | 0.137 | 0.015 |
| A2 Time [ms] | 21.881 | 0.455 |
| A2 Velocity [m/s] | -0.287 | 0.040 |
| HC Time [ms] | 17.117 | 0.393 |
| Peak Dist, [mm] | 5.194 | 0.309 |
| Radius [mm] | 6.562 | 0.645 |
| A1 Deformation Amp, [mm] | 0.138 | 0.009 |
| HC Deformation Amp, [mm] | 1.132 | 0.133 |
| A2 Deformation Amp, [mm] | 0.343 | 0.072 |
| A1 Deflection Length [mm] | 2.315 | 0.149 |
| HC Deflection Length [mm] | 6.784 | 0.527 |
| A2 Deflection Length [mm] | 2.885 | 0.739 |
| A1 Deflection Amp, [mm] | 0.094 | 0.007 |
| HC Deflection Amp, [mm] | 0.998 | 0.137 |
| A2 Deflection Amp, [mm] | 0.109 | 0.011 |
| Deflection Amp, Max [mm] | 1.014 | 0.137 |
| Deflection Amp, Max [ms] | 16.619 | 0.704 |
| Whole Eye Movement Max [mm] | 0.241 | 0.070 |
| Whole Eye Movement Max [ms] | 22.121 | 0.811 |
| A1 Deflection Area [mm²] | 0.179 | 0.023 |
| HC Deflection Area [mm²] | 3.725 | 0.729 |
| A2 Deflection Area [mm²] | 0.249 | 0.066 |
| A1 dArc Length [mm] | -0.019 | 0.003 |
| HC dArc Length [mm] | -0.145 | 0.030 |
| A2 dArc Length [mm] | -0.023 | 0.006 |
| dArcLengthMax [mm] | -0.166 | 0.036 |
| Max InverseRadius [mm^-1] | 0.189 | 0.017 |
| DA Ratio Max (2mm) | 4.093 | 0.393 |
| PachySlope [μm] | 34.814 | 11.435 |
| DA Ratio Max (1mm) | 1.530 | 0.048 |
| ARTh | 731.025 | 322.529 |
| bIOP | 14.295 | 2.693 |
| Integrated Radius [mm^-1] | 8.769 | 1.045 |
| SP A1 | 121.344 | 21.994 |
| CBI | 0.202 | 0.299 |
| TBI | 5.805 | 2.346 |
| SSI | 0.075 | 0.256 |
| CBI_LVC | 0.015 | 0.113 |

**Table 4. Significant differences founder in the different comparisons: between mCNV eyes and non-mCNV eyes, between MBMH eyes and non-MBMH eyes and between FM eyes and non-FM eyes.**

| | mCNV EYES | | non-mCNV EYES | | |
|---|---|---|---|---|---|
| **Student t-test** | **Mean** | ***SD*** | **Mean** | **SD** | ***p*** |
| HC Time [ms] | 17.027 | 0.414 | 17.210 | 0.352 | 0.069 |
| | **MBMH EYES** | | **non-MBMH EYES** | | |
| **Student t-test** | **Mean** | ***SD*** | **Mean** | **SD** | ***p*** |
| Whole eye movement max [ms] | 22.450 | 0.719 | 21.836 | 0.763 | 0.030 |
| TBI | 6.809 | 0.627 | 5.321 | 2.597 | 0.046 |
| Hours per week of physical activity (hours) | 2.89 | 2.54 | 0.81 | 1.91 | 0.024 |
| **Pearson Chi-Square test** | | | | | ***p*** |
| Physical activity (%) | 73.3 | | 31.3 | | 0.020 |
| Outdoor physical activity (%) | 80.0 | | 21.4 | | 0.006 |
| Sunglasses less than half of time (%) | 73.3 | | 23.1 | | 0.025 |
| | **FM EYES** | | **non-FM EYES** | | |
| **Student t-test** | **Mean** | ***SD*** | **Mean** | **SD** | ***p*** |
| Weigth (kg) | 69.28 | 10.01 | 60.38 | 11.88 | 0.032 |

CNV: myopic choroidal neovascular membrane; MBMH: macular Bruch membrane hole; FM: foveal/perifovealmembrane.

**Table 5. Description of Spearman's rank moderate-to-strong correlation coefficients between corneal biomechanical parameters and demographic, biometric, lifestyle, tomographic and treatment-related data.**

| | | Age | High | Weigth | Axial length | White-To-White | Hours per week of physical activity | Open air hours per day | Annual beach days | Times per day of eye rubbing | Daily cell-phone hours | Daily reading hours | Daily TV hours | Daily PC hours | Membrane diameter | Number of intravitreal anti-VEGF injections | Treatment length |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Def, Amp, Max [mm] | **CC** | 0.090 | -0.083 | -0.157 | -0.362 | -0.370 | -0.011 | 0.091 | -0.148 | -0.101 | -0.108 | **-0.385*** | 0.032 | -0.208 | 0.073 | 0.014 | 0.031 |
| | ***p*** | 0.643 | 0.668 | 0.416 | 0.116 | 0.057 | 0.960 | 0.651 | 0.454 | 0.616 | 0.599 | **0.039** | 0.867 | 0.279 | 0.719 | 0.941 | 0.872 |
| A1 Velocity [m/s] | **CC** | -0.144 | 0.006 | -0.139 | -0.329 | -0.173 | 0.250 | **0.395*** | 0.105 | 0.165 | 0.192 | -0.255 | -0.137 | 0.126 | 0.127 | 0.164 | 0.132 |
| | ***p*** | 0.455 | 0.975 | 0.472 | 0.157 | 0.389 | 0.228 | **0.042** | 0.593 | 0.412 | 0.349 | 0.182 | 0.477 | 0.516 | 0.527 | 0.394 | 0.495 |
| HC Deformation Amp, [mm] | **CC** | 0.090 | -0.083 | -0.157 | -0.362 | -0.370 | -0.011 | 0.091 | -0.148 | -0.101 | -0.108 | **-0.385*** | 0.032 | -0.208 | 0.073 | 0.014 | 0.031 |
| | ***p*** | 0.643 | 0.668 | 0.416 | 0.116 | 0.057 | 0.960 | 0.651 | 0.454 | 0.616 | 0.599 | **0.039** | 0.867 | 0.279 | 0.719 | 0.941 | 0.872 |
| A2 Deformation Amp, [mm] | **CC** | 0.257 | 0.211 | -0.106 | -0.093 | -0.339 | 0.127 | 0.021 | -0.114 | -0.201 | 0.091 | -0.097 | -0.256 | 0.053 | **0.404*** | -0.012 | -0.157 |
| | ***p*** | 0.178 | 0.273 | 0.584 | 0.696 | 0.084 | 0.547 | 0.917 | 0.563 | 0.315 | 0.658 | 0.615 | 0.179 | 0.787 | **0.037** | 0.950 | 0.416 |
| A2 Deflection Amp, [mm] | **CC** | 0.166 | 0.092 | -0.028 | -0.253 | -0.047 | -0.061 | -0.154 | -0.090 | -0.150 | 0.065 | **-0.424*** | -0.097 | 0.008 | 0.028 | -0.221 | -0.355 |
| | ***p*** | 0.389 | 0.636 | 0.885 | 0.281 | 0.817 | 0.773 | 0.445 | 0.649 | 0.456 | 0.752 | **0.022** | 0.615 | 0.968 | 0.888 | 0.250 | 0.059 |
| Deflection Amp,Max [mm] | **CC** | 0.087 | -0.135 | -0.038 | -0.268 | -0.269 | 0.100 | 0.114 | -0.239 | -0.028 | -0.177 | **-.370*** | 0.129 | -0.236 | -0.023 | 0.014 | 0.073 |
| | ***p*** | 0.652 | 0.485 | 0.843 | 0.254 | 0.175 | 0.634 | 0.571 | 0.222 | 0.889 | 0.386 | **0.048** | 0.504 | 0.218 | 0.911 | 0.944 | 0.707 |
| Deflection Amp. Max [mm] | **CC** | 0.244 | 0.201 | -0.139 | -0.075 | -0.343 | 0.141 | 0.069 | -0.119 | -0.214 | 0.116 | -0.082 | -0.264 | 0.058 | **.396*** | -0.017 | -0.150 |
| | ***p*** | 0.201 | 0.295 | 0.471 | 0.753 | 0.080 | 0.501 | 0.734 | 0.545 | 0.284 | 0.571 | 0.671 | 0.167 | 0.767 | **0.041** | 0.929 | 0.436 |
| Whole Eye Movement Max [ms] | **CC** | 0.279 | 0.272 | -0.029 | **-0.447*** | **-0.411*** | 0.124 | -0.120 | -0.139 | 0.076 | 0.048 | 0.105 | -0.017 | 0.038 | 0.341 | 0.095 | 0.057 |
| | ***p*** | 0.142 | 0.153 | 0.883 | **0.048** | **0.033** | 0.556 | 0.552 | 0.481 | 0.708 | 0.815 | 0.589 | 0.929 | 0.843 | 0.081 | 0.622 | 0.768 |
| A2 Deflection Area [mm²] | **CC** | 0.142 | 0.041 | 0.090 | -0.083 | 0.007 | 0.099 | -0.025 | -0.217 | -0.315 | -0.013 | -0.227 | -0.208 | -0.151 | -0.153 | -0.271 | **-0.384*** |
| | ***p*** | 0.461 | 0.831 | 0.642 | 0.729 | 0.972 | 0.636 | 0.900 | 0.266 | 0.110 | 0.949 | 0.236 | 0.280 | 0.434 | 0.445 | 0.156 | **0.039** |
| A1 dArc Length [mm] | **CC** | -0.014 | -0.022 | -0.112 | -0.133 | -0.264 | **-0.405*** | 0.051 | 0.002 | -0.192 | -0.236 | -0.072 | -0.010 | -0.181 | 0.081 | 0.070 | -0.010 |
| | ***p*** | 0.945 | 0.908 | 0.563 | 0.575 | 0.183 | **0.044** | 0.799 | 0.992 | 0.338 | 0.247 | 0.710 | 0.957 | 0.349 | 0.687 | 0.717 | 0.961 |
| HC dArc Length [mm] | **CC** | -0.115 | 0.091 | 0.176 | 0.335 | **0.421*** | -0.082 | 0.028 | 0.298 | -0.177 | 0.210 | **0.459*** | -0.035 | 0.071 | -0.159 | -0.050 | -0.097 |
| | ***p*** | 0.553 | 0.638 | 0.361 | 0.149 | **0.029** | 0.698 | 0.888 | 0.124 | 0.376 | 0.304 | **0.012** | 0.857 | 0.713 | 0.429 | 0.797 | 0.616 |
| A2 dArc Length [mm] | **CC** | -0.161 | -0.035 | 0.043 | -0.045 | 0.118 | -0.219 | -0.016 | 0.291 | 0.217 | 0.054 | 0.284 | 0.270 | 0.076 | 0.065 | 0.279 | 0.387* |
| | ***p*** | 0.404 | 0.856 | 0.825 | 0.852 | 0.558 | 0.293 | 0.938 | 0.133 | 0.277 | 0.793 | 0.136 | 0.157 | 0.694 | 0.749 | 0.142 | 0.038 |
| dArcLength-Max [mm] | **CC** | -0.145 | 0.140 | 0.251 | 0.307 | **0.533**** | -0.158 | 0.063 | 0.198 | -0.008 | -0.063 | **0.402*** | 0.057 | -0.026 | -0.216 | -0.032 | -0.014 |
| | ***p*** | 0.453 | 0.469 | 0.188 | 0.188 | **0.004** | 0.450 | 0.756 | 0.312 | 0.968 | 0.760 | **0.030** | 0.768 | 0.895 | 0.280 | 0.869 | 0.942 |
| ARTh | **CC** | -0.177 | -0.021 | -0.242 | **.472*** | **.386*** | 0.256 | 0.222 | 0.302 | 0.094 | 0.106 | 0.276 | -0.085 | 0.085 | 0.151 | 0.159 | 0.104 |
| | ***p*** | 0.357 | 0.912 | 0.205 | **0.036** | **0.047** | 0.216 | 0.265 | 0.118 | 0.641 | 0.607 | 0.148 | 0.661 | 0.661 | 0.451 | 0.410 | 0.590 |
| Integrated Radius [mm^-1] | **CC** | -0.010 | 0.014 | 0.156 | **-0.483*** | -0.171 | -0.164 | -0.055 | -0.049 | -0.159 | -0.035 | -0.193 | -0.110 | -0.211 | -0.233 | -0.054 | -0.024 |
| | ***p*** | 0.961 | 0.943 | 0.419 | **0.031** | 0.395 | 0.433 | 0.786 | 0.804 | 0.430 | 0.865 | 0.316 | 0.568 | 0.272 | 0.242 | 0.779 | 0.901 |
| CBI | **CC** | 0.168 | -0.033 | 0.207 | **-0.511*** | **-0.406*** | -0.204 | -0.222 | -0.291 | -0.084 | -0.082 | -0.259 | -0.007 | -0.096 | -0.112 | -0.045 | 0.037 |
| | ***p*** | 0.383 | 0.863 | 0.281 | **0.021** | **0.036** | 0.329 | 0.265 | 0.133 | 0.677 | 0.691 | 0.174 | 0.973 | 0.619 | 0.578 | 0.819 | 0.850 |
| TBI | **CC** | 0.162 | 0.010 | -0.218 | **0.475*** | 0.070 | 0.336 | 0.329 | -0.077 | 0.007 | -0.243 | **0.404*** | 0.183 | -0.013 | 0.128 | 0.061 | -0.022 |
| | ***p*** | 0.402 | 0.957 | 0.257 | **0.034** | 0.727 | 0.100 | 0.094 | 0.695 | 0.972 | 0.231 | **0.030** | 0.342 | 0.947 | 0.526 | 0.753 | 0.910 |

CC: correlation coefficient

Treatment related data are described in Table 2.

The mean AL was 24.4±2.5 mm and mean CCT was 550 µm. Total sample biometric and biomechanical data are expressed in Table 3.

A comparison between mCNV eyes and non-mCNV eyes was made regarding demographic, biometric, ocular biometric, anatomic, biomechanical, lifestyle and treatment-related parameters. After, the same comparisons were made within two subgroups of mCNV eyes: between MBMH eyes and non-MBMH eyes and between FM eyes and non-FM eyes. Table 4 highlights the significant differences found in these comparisons regarding all the addressed parameters.

Relationships between corneal biomechanics and all other parameters were studied and Table 5 summarizes those founded to be at least moderate in strength.

A multivariable logistic regression model confirmed the independent effect WEM Max time and TBI on the presence of MBMH with an AUROC in the ROC analysis (AUROC) for this model of 0.808 (Fig. 1).

Conditional estimates plots for HC-time effect on the probability of mNVC and for each of the variable within the logistic regression model regarding the presence of MBMH were build and are shown in Fig. 1.

## DISCUSSION

The present work was aimed to make a comparison between mCNV eyes and non-mCNV eyes regarding in vivo corneal biomechanical assessment. Within mCNV eyes, the subgroups of those with MBMH (47%) and those with FM (59%) were analyzed. Secondary purpose was to address predictors - biometric, biomechanical, demographic and lifestyle – of disease and treatment response.

The present study is centered in corneal biomechanics analysis of a population of subjects with unilateral mNVC. In this setting, the HC-time was the only biomechanical parameter showing a tendency to be significantly different in eyes with mNVC and no other differences were found. Theoretically this is one of the most important single-parameter, as aforementioned, and lower values, as in mNVC eyes in this study, can be associated with a less rigid tissue behavior. However, when a multivariable logistic regression biomechanical model was tried to differentiate eyes with and without mNVC, it was impossible to reach acceptable AUROCs. Besides some recent descriptions of Corvis ST® parameters in myopia,[15,16] to the authors knowledge, this is the first study specifically in eyes with mCNV. The authors

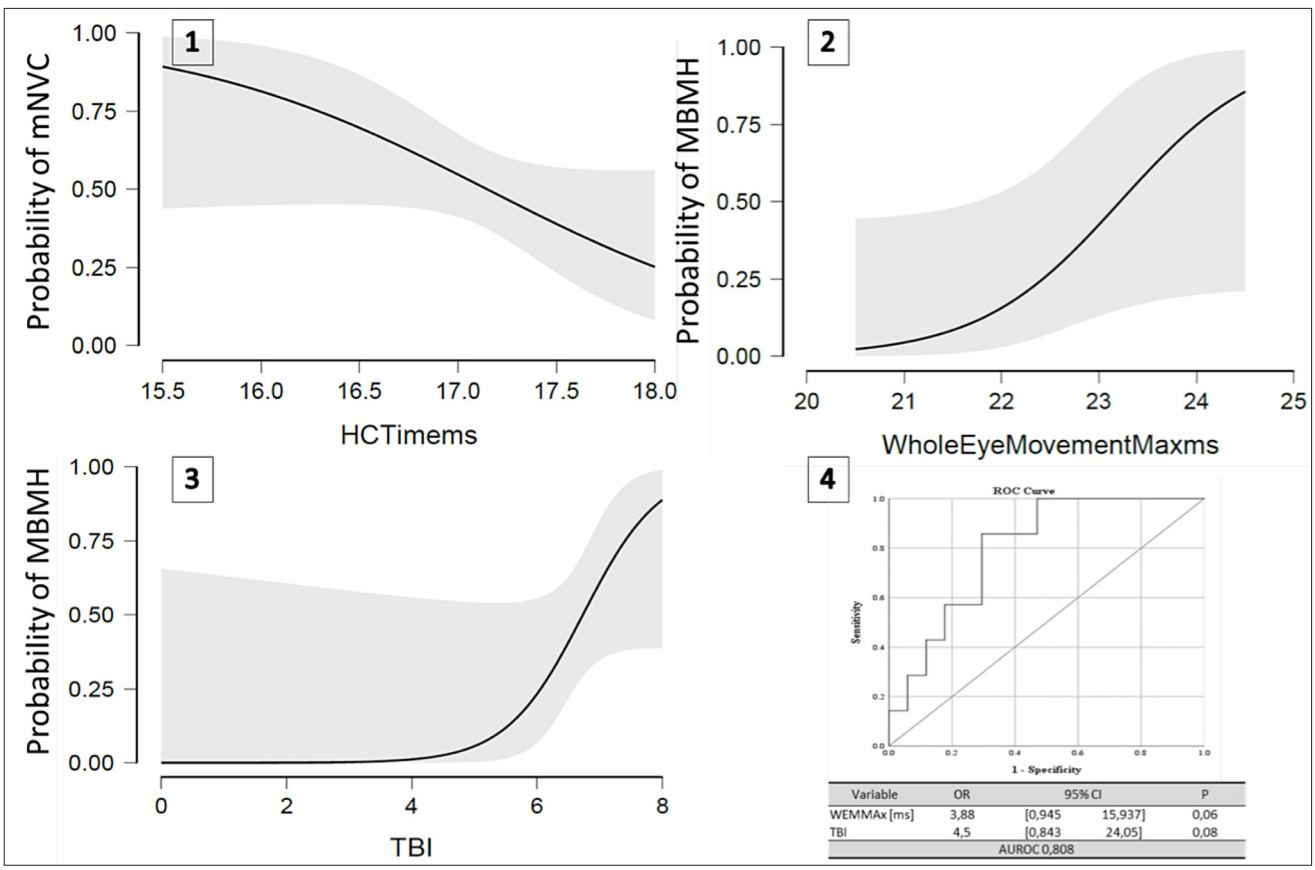



Figure 1. Composed figure: 1: Conditional estimates plot for HC-time effect on the probability of mNVC; 2 and 3: Conditional estimates plots for WEM Max Time and TBI effect on the probability of MBMH; 4: ROC curve of the multivariable biomechanical model to predict the presence of MBMH, with the included variables and respective AUROC.

mCNV: myopic choroidal neovascular membrane; MBMH: macular Bruch membrane hole.

postulate that these membranes are multifactorial, being more difficult to build a pure mechanical model, with the number of eyes present in this study.

MBMH are described as specific chorioretinal barrier mechanical alterations, a distinct form of chorioretinal atrophy with high risk of mCNV formation.[1,9,10] Within the MBMH subgroup analysis in the present work, the WEM Max Time and TBI were found to be significantly higher without differences in AL or c-IOP, leading us to two different theoretical assumptions: first, the prove that eyes with larger antero-posterior deflexion of the lateral cornea may be transmitting more energy directly to the posterior pole, acting as continuous blunt micro traumas over time, and causing ruptures in Bruch's membrane; second, as Bruch membrane and cornea are both made mainly of collagen, MBMH could be part of the spectrum of tissue susceptibility to mechanical deformation, as described by higher TBI values in the corneal ectasia setting and TBI itself could be studied in the future as a marker of posterior pole fragility. A multivariable logistic regression could be built in the present study, including these parameters, with an AUROC of 0.808 to differentiate mCNV eyes with or without MBMH and to the authors knowledge this is the first report of a corneal biomechanics-based prediction model of a mechanical alteration in the posterior pole, namely in myopia setting. Additionally, the absence of effect from age, AL, corvis derived-IOP or corvis derived-bIOP make it even more valuable, as a purely biomechanical model.

Additionally to known lower CCT, theoretically, it is expected that eyes with less stiffness were associated to higher values on the deformation and deflection amplitudes, deflection areas and applanation lengths in all timepoints, lower A1T with higher A1V but higher A2T with lower A2V, lower MaxDT and higher peak distance (HCPD) and lower radius (HCR) when the cornea is in the highest concavity timepoint (HCT).[17,18] Within the setting of a single-parameter analysis, the A1T, A2T and HC-related parameters were the first described as the most important. On the other hand, deflection areas were thought to be less important parameters within this basic analysis.[17,18] Besides the comprehensive limitations of single parameters to describe the complex biomechanical behavior, they are affected by IOP (otherwise none of the air-puff tonometers would work). Nevertheless, large amount of data from all these aforementioned parameters began to be studied through various methods towards the construction of models of characterization of increasing consistency and 2nd generation parameters are in constant evolution nowadays.[17] The Stiffness parameter in A1 (SP-A1), created by the group of Roberts *et al*[19] was defended as the most accurate in defining the global eye rigidity, including the relation of IOP with both corneal and scleral biomechanical components. Moreover, the CBI was built by Vinciguerra *et al*[20] as an exponential function score made through a logistic regression analysis of 6 DCR parameters and adjusted for IOP and CCT and is defended as the most embracing corneal biomechanical descriptor in the ectasia setting. Nevertheless, even more recent is the Stress Strain Index (SS-I), built by finite element modeling and validated as the newest and most accurate algorithm for the estimation of the non-linear in vivo biomechanical behavior in corneas with normal topography.[21] To address ectasia risk there was a need to go further and Ambrósio Jr *et al*[22] combined data from corneal deformation response, including CBI, with tomographic data, through artificial intelligence and developed a more accurate index, the tomographic and biomechanical index (TBI). The Whole eye movement (WEM) concept should be explained differentially: it refers to the antero-posterior excursion the cornea exhibits in the most lateral part of each side of the 8 mm Scheimpflug image. Although not proven yet, the authors believe that the WEM could be of great value in the study of posterior pole pathology in myopic eyes as it is assumed to describe the accessorial movement occurring in the rest of the eye after the transmission of energy that the cornea could not absorb in its movement.[17] It is characterized by length and duration of the movement and remains unclear if can be related to scleral stiffness. Nevertheless, besides proven repeatability,[23,24] care needs to be taken in all these assumptions due to the lack of external validation in different populations and ocular status, like the myopic eye.

The prevalence of mCNV in myopic eyes can reach 5%-10%. Although typically these membranes are less than 1000 um in diameter,[25] we found an average value of 1168.5 μm, with no significant differences in the subgroups analysis and no correlations with lifestyle factors. However, larger membranes correlate with two biomechanical parameters, including the WEM max length, in the direction of softer behavior. Analyzing treatment-related data, we found a mean number of nearly 8 intravitreal injections within a mean treatment interval of 28.5 months. In comparison, the group 1 of the RADIANCE Study,[26] with a similar protocol, needed 4 injections in average at 12 months, with a proportion of 65% of resolution over this period. Although we did not find moderate or strong correlations between lifestyle habits and disease-related or treatment-related parameters, when correlating with biomechanical data, treatment length was correlated with two biomechanical parameters. Although these findings have not yet consistency and the variability of treatment duration limits the associations between treatment exposure and the other factors, to the authors knowledge this is the first report of an association between ocular biomechanics and mNVC anatomy or intravitreal treatment and we believe that this may be the beginning of a path that aggregates the dynamic study of the eye as a predictor of long-term prognosis to other static predictors recently described.[27]

Regarding ocular biometric data, normal values of W-T-W and CCT were found, and the mean AL was of 24.4 mm, under the definition of HM. We did not find significant differences regarding AL both in the comparison between mCNV eyes and non-mCNV eyes and in the subgroup analysis. Moreover, moderate correlations were found between AL and four biomechanical parameters - positive with TBI and Radius and negative with max inverse radius and CBI – which are not all in the same way in terms of eye

stiffness, according to the basic corneal biomechanical concepts explained downwards. In fact, recent literature has described a non-linear relationship between axial length and corneal biomechanics for different AL ranges[28,29] and all the aforementioned is proof that the classic anatomical view of axial elongation as the main risk factor for myopia-associated chorioretinal degeneration should be reviewed and, probably, integrated into a new risk assessment paradigm, aggregating static and dynamic measurements.

The association of axial myopia progression and lifestyle factors like near work,[30] outdoor activity[31] or physical activity[32] are being subject of many studies over the time. Although not completely consensual, there are good evidence about the importance of this factors in myopia progression. However, data is scarce regarding the mCNV setting. The questionnaire implemented in the present study served to characterize this myopic population with unilateral mCNV in relation to lifestyle factors that the authors believe may influence the ocular biomechanical state and, therefore, the risk of mCNV. Nearly half of subjects reported regular physical activity, mainly walking and nearly three daily hours were spend doing open air activities with nearly 44% of them using sunglasses for less than half of time, in average. We found that mCNV eyes with MBMH belonged to subjects with significantly higher proportion of physical activity, specifically outdoor, and less than half of time sunglasses wearing pattern. Although the documented preventive role of outdoor activity in myopia progression,[33,34] physical activity should be analyzed with caution in myopic subjects. In fact, a recent overview of systematic reviews and meta-analyses showed time spent outdoors but no physical activity to have a protective role in myopia progression[35] and the authors postulate that although more sun exposure could promote natural corneal and scleral crosslinking, physical activity could induce cumulative microtrauma, which could be associated with mechanical degeneration of the posterior pole. In other way, higher UV-light exposure – expressed through the variable *sunglasses less than half of time* – could promote a high ratio of corneal/scleral cross-linking, leading to less capacity of energy absorption by the cornea and more deleterial energy from cumulative microtrauma being transmitted to the posterior pole (as explained within the WEM concept downwards). To the authors knowledge, this is the first literature description of these concepts. During the COVID-19 pandemic there was an acceleration of the myopic progression in children and the home quarantine-driven increased use of digital screen devices was the main suspect.[36] However, the present study did not find significant differences in the near work-related habits (*daily hours spend on the cellphone, PC, TV* or *reading* variables) between subjects with and without MBMH in the mCNV eye. Additionally, correlations between membrane diameter and any of the aforementioned lifestyle factors were not found.

Another two factors that the authors hypothesized in the present study to be associated with mCNV are eye rubbing and sleeping position related habits. Regarding the first, although this association was recently described in the keratoconus setting by the group of Gatinel,[37] to the authors knowledge, it was not described yet for the axially elongated myopic eye. In the present study, nearly 43% of subjects reported eye rubbing habits, with 2.7 times per day in average, but there were no significant differences, namely between subjects with and without MBMH. The questionnaire comprised the question regarding which eye had more rubbing, but most individuals did not answer this question and therefore it was not included. Regarding the second, the present study did not found more prevalence of mCNV or MBMH in the side in which individuals sleep on, but the answer missing rate was high in this parameter too, precluding conclusions.

The present study tried to find correlations between biomechanical parameters and both demographic and lifestyle data. Some moderate or strong correlations were found between biomechanical parameters and lifestyle habits: *physical activity weekly hours* and *daily outdoor activity hours* were correlated with one biomechanical parameter each, and *daily reading hours* was correlated with seven biomechanical parameters. As aforementioned, the biomechanical characterization is complex, and one should look it as a whole instead of a single-parameter approach. In this sense, these results corroborate some literature[38] highlighting the need for introduce lifestyle factors when we study corneal biomechanics. In fact, knowing how the environment and some life habits can modulate the biomechanics of ocular tissues is the first step towards being able to practice preventive medicine in the myopia epidemics. The authors believe that studies such as the present one, associated with the in vitro evolution of potential treatments,[39] should walk side by side towards the construction of new strategies capable of prevent and treat the deleterious consequences of progressive myopia, such as myopic neovascularization.

Regarding demographic data, the proportion of females in our sample was significantly higher than males, which can be associated to hormonal factors[40] or in vitro fertilization.[41] Regarding clinical data, the proportion of autoimmune diseases in our sample, namely thyroid disease should be highlighted but, although inflammatory factors were thought to be involved in the pathogenesis of idiopathic choroidal neovascularization,[42] there are no consistent data about its role in mCNV.

This study included 50% of pseudophakic eyes, with cataract surgery more than 1 year before. In fact, some literature reports describe changes in corneal biomechanics 3 months after surgery[43,44] but to the authors knowledge there are no reports on the possible long-term effects. However, as all were bilateral and with similar proportion both in eyes with and without MBMH, we believe this is not an important limitation in the present study. Additionally, the proportion of pseudophakic eyes is the reason why anterior chamber depth was not included in the analysis as another biometric descriptor.

Finally, the authors believe that corneal biomechanics can have a role in systemic physiology and pathology in the future as a rapid, non-invasive and reproducible biomarker, acting like a *tissue dynamic behavior fingerprint*. The re-

lationship between corneal biomechanics and whole body biometric parameters or even diet has been described in literature.[45] Although in the present study corneal biomechanics did not correlate with height or weight, in our sub analysis, the subgroup of eyes with FM belonged to heavier individuals and this is an example of an ocular-systemic link to explore in the future.

The small sample underpowers the study and it impairs finding differences between groups. It would be interesting to see if a larger model would reach statistical significance in biomechanical parameters more associated to global eye biomechanics other than WEM, namely in SP-A1 and SS-I. Additionally, with a larger sample and 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, as it is unknown if the non-mCNV eyes or the ones without MBMH will develop it with time. A longitudinal study would therefore be appropriate to reach a more consistent mNVC risk prediction.

The added value of the study is its conceptual and innovative character, studying a pathology with an increasing global health burden in young and active individuals from a perspective never approached before and bringing information that, in the authors' point of view, could pave the way for a more dynamic view of the eye, both in pathology and in disease, namely using the myopic eye as a paradigm.

## CONCLUSION

To the authors knowledge, this is the first study evaluating in vivo ocular biomechanics in mCNV. Through a pure biomechanical model including WEM Max Time and TBI without the influence of AL or IOP, corneal biomechanical assessment by means of Scheimpflug image showed promising results as a predictor of mCNV, more specifically of macular Bruch Membrane holes, with an AUROC of 0.808 and this could be modulated in part by lifestyle factors like physical activity and sun exposure. Future studies should be performed to confirm our findings, paving the way to the introduction of a dynamic paradigm which could replace the current static one in mCNV risk assessment of myopic eyes.

## CONTRIBUTORSHIP STATEMENT / DECLARAÇÃO DE CONTRIBUIÇÃO:

The authors confirm contribution to the paper as follows:

Study conception and design: Pedro Manuel Baptista; João Heitor Marques; Angelina Meireles; Renato Ambrósio Jr; Pedro Menéres; João Melo Beirão.

Data collection: Pedro Manuel Baptista; João Heitor Marques; Paulo Sousa; Saul Pires.

Analysis and interpretation of results: Pedro Manuel Baptista; João Heitor Marques; Maria João Furtado; Miguel Ribeiro Lume; Angelina Meireles; Renato Ambrósio Jr; Pedro Menéres; João Melo Beirão.

Draft manuscript preparation: Pedro Manuel Baptista; João Heitor Marques.

All authors reviewed the results and approved the final version of the manuscript.

## RESPONSABILIDADES ÉTICAS

**Conflitos de Interesse:** Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.

**Fontes de Financiamento:** Não existiram fontes externas de financiamento para a realização deste artigo.

**Confidencialidade dos Dados:** Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.

**Proteção de Pessoas e Animais:** Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pela Comissão de Ética responsável e de acordo com a Declaração de Helsínquia revista em 2013 e da Associação Médica Mundial.

**Proveniência e Revisão por Pares:** Não comissionado; revisão externa por pares.

## ETHICAL DISCLOSURES

**Conflicts of Interest:** The authors have no conflicts of interest to declare.

**Financing Support:** This work has not received any contribution, grant or scholarship.

**Confidentiality of Data:** The authors declare that they have followed the protocols of their work center on the publication of data from patients.

**Protection of Human and Animal Subjects:** The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki as revised in 2013).

**Provenance and Peer Review:** Not commissioned; externally peer reviewed.

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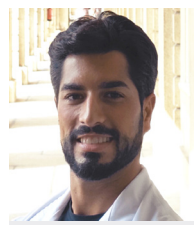

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