The Association between the Pulsatile Choroidal Volume Change and Ocular Rigidity

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Purpose: To assess the relationship between the pulsatile choroidal volume change (ΔV) and ocular rigidity (OR), an important biomechanical property of the eye.

Design: This is a prospective cross-sectional study.

Subjects: Two hundred seventeen participants (235 eyes) were included in this study. Of those, 18 eyes (18 participants) had exudative retinal disease, and 217 eyes (199 participants) had open-angle glaucoma (39.2%), suspect discs (12.4%), ocular hypertension (14.3%), or healthy eyes (34.1%).

Methods: Pulsatile choroidal volume change was measured using dynamic OCT, which detects the change in choroidal thickness during the cardiac cycle. Ocular rigidity was measured using an invasive procedure as well as using a validated optical method. Correlations between ΔV and OR were assessed in subjects with healthy eyes, eyes with glaucoma, or eyes with exudative retinal disease.

Main Outcome Measures: Ocular rigidity and pulsatile ocular volume change.

Results: In 18 eyes where OR was obtained invasively and ΔV was obtained noninvasively, a significant correlation was found between ΔV and OR ($r_s = -0.664$, $P = 0.003$). Similarly, a strong inverse correlation was found between the noninvasive measurements of both ΔV and OR ($r_s = -0.748$, $P < 0.001$) in a large cohort and maintained its significance across diagnostic groups (a more compliant eye is associated with greater ΔV). No correlation was found between ΔV and age, blood pressure, intraocular pressure, axial length, or diagnosis ($P \geq 0.05$). Mean ΔV was 7.3 ± 3.4 μL for all groups combined with a range of 3.0 to 20.8 μL.

Conclusions: These results suggest an association between the biomechanics of the corneoscleral shell and pulsatile ocular blood flow, which may indicate that a more rigid eye exerts more resistance to pulsatile choroidal expansion. This highlights the dynamic nature of both blood flow and biomechanics in the eye, as well as how they may interact, leading to a greater understanding of the pathophysiology of ocular disease.

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Glaucoma is a multifactorial disease characterized by damage to the retinal ganglion cells' axons and visual field loss. It is the leading cause of irreversible blindness globally. Despite investigative efforts to elucidate the relationship between ocular rigidity (OR) and the pathophysiology of primary open-angle glaucoma (POAG), our understanding of this association remains limited. The biomechanical paradigm of glaucoma postulates that elevated mechanical stress and strain lead to axonal damage and retinal ganglion cell loss.[1–3] A growing body of evidence indeed suggests that scleral stiffness, the major contributor to the rigidity of the corneoscleral shell, is the most determining factor for stress and strain at the optic nerve head (ONH) (more so than intraocular pressure [IOP])[4,5] and that lower OR (or a more compliant sclera) may be associated with glaucoma.[4,6–9] There is also evidence that ocular blood flow plays an important role in the pathophysiology of glaucoma.[10] However, it has been proposed that the mechanical and vascular mechanisms of glaucoma

are intertwined in determining the susceptibility to developing glaucomatous optic neuropathy.[11,12] The geometrical and material properties of the sclera and lamina cribrosa, through which blood vessels must pass, could affect the vasculature (and perfusion) of the eye.

The sclera, as a relatively closed shell, could also constrain the expansion of the choroid during systole to a greater or lesser amount depending on its stiffness because it requires more force to expand during systole if the sclera is stiffer. In fact, recent biomechanical modeling has predicted exactly this phenomenon, but it has not been validated clinically.[13] In addition, basic physiology links increased rigidity of blood vessels to reduced pulsatile volume.[14] As the stiffness of an artery wall increases, the pulse volume of blood in the artery decreases, if other factors are constant.[14]

The intimate relationship between biomechanics and ocular blood flow is evidenced by a number of studies. For example, subjects with vasospasticity, a known risk factor in glaucoma, were found to exhibit an abnormal vascular

regulatory response to biomechanical stimuli[15−20] in addition to temperature and emotional stress.[21] More recently, low OR was shown to be significantly associated with greater glaucomatous retinal nerve fiber layer damage in patients with vasospasm.[22]

It is evident that short-term and long-term IOP changes [23] induce mechanical stress and strain on the ONH.[11,12] Pulsatile IOP changes also induce ONH stresses and strains, which are smaller but which repeat 90 000 times per day.[13] Their role is under investigation.[24,25] Here we examine how the rigidity of the corneoscleral shell might affect the pulsatility of the eye. We hypothesize that there may be an association between the biomechanics of the corneoscleral shell and the ocular blood flow in such a way that the rigidity of the eye could limit the amount of pulsatile blood entering the choroid. The purpose of this study, then, is to assess the relationship between the pulsatile choroidal volume change (ΔV) and OR.

Methods

This study followed the tenets of the Declaration of Helsinki and was approved by the Maisonneuve-Rosemont Hospital institutional review board. Written informed consent was obtained from all subjects prior to testing.

Pulsatile choroidal volume change was measured using dynamic submacular OCT imaging. The details of the method are described in previous studies by our group[26,27] and are illustrated in Figure 1. In brief, a video of the choroid is acquired at 8 Hz using the Spectralis OCT (Heidelberg Engineering) in enhanced depth imaging mode, and the heart rate is measured simultaneously using an oximeter. Choroidal images (30° wide b-scans) are processed using an automated segmentation algorithm that detects the Bruch membrane and the choroid-sclera interface.[26,28] In each frame, choroidal thickness is measured, and then the pulsatile choroidal thickness change is computed over the time-series. An individualized mathematical 2-spheres model of the eye (accounting for ocular axial length [AL]) is then used to extrapolate the ΔV from pulsatile choroidal thickness change.[27] Using the Lomb−Scargle periodogram, the subject's heart rate frequency serves to confirm that the choroidal thickness fluctuations in the time-series correspond to the rate of choroidal filling.

The Friedenwald's OR function describes the pressure−volume relationship as [29]:

$$\ln \frac{IOP}{IOP_0} = OR * (V - V_0)$$

where a high OR value represents a rigid eye, and vice versa. This function is used to compute the OR coefficient. In this study, we measured OR invasively in a smaller cohort and noninvasively in a larger cohort of subjects. Invasive OR was obtained in eyes requiring intravitreal injections for therapeutic indications using the Friedenwald equation. Measurement of IOP using a portable tonometer (Tono-Pen XL, Reichert Technologies) was performed before and immediately after 50 μL of bevacizumab was

injected intravitreally in these eyes with exudative retinal diseases.[30] Noninvasive OR was obtained using an optical method as described here.[26,27] The pulsatile change in IOP is measured by Dynamic Contour Tonometry (Ziemer Ophthalmic Systems AG). Both ΔV and OR measurements were shown to have good repeatability (intraclass correlation coefficient was 0.920, 95% confidence interval [0.865, 0.952] and 0.942, 95% confidence interval [0.820, 0.982], respectively), and the noninvasive measurement of OR was highly correlated with an invasive measurement of OR in the same eyes.[27]

Adult subjects with POAG, suspect discs, ocular hypertension (OHT), or healthy eyes were recruited sequentially from the Maisonneuve Rosemont Hospital Ophthalmology Glaucoma Clinic. All subjects underwent a complete eye examination, including IOP measurements by Goldmann applanation tonometry, iridocorneal angle and optic disc assessment, OCT imaging, and visual field (VF) testing. Healthy eyes were characterized as having untreated IOP <21 mm Hg, normal optic disc appearance on fundus exam, and normal VF. Eyes with OHT had IOP ≥24 mm Hg on 3 separate visits, normal optic disc appearance, and normal VF. Eyes with suspect discs presented with normal or elevated IOP, increased or asymmetric cup-to-disc ratio (suspicious optic nerve appearance), with no detectable structural damage on OCT and no repeatable VF loss. Eyes with POAG were defined as having glaucomatous optic nerve appearance, and repeatable structural and/or functional loss with OCT imaging and/or VF (Zeiss Humphrey Systems) testing (SITA standard threshold 24-2 strategy). All eyes had open (nonoccludable) angles on gonioscopy, clear media and no other eye disease, including no signs of secondary glaucoma or retinopathy. Subjects with known systemic collagen disease and those with unstable fixation were excluded.

Medical records were reviewed, and medical history was obtained from questioning participants about their health. In addition to ΔV and OR measurements, the brachial blood pressure was measured using an automated sphygmomanometer (Welch Allyn Inc) following OR measurement.

Descriptive analyses of baseline demographics were carried out using SPSS statistical software (version 27; SPSS, Inc). Correlations between ΔV, OR, and other clinical measurements were assessed in all eyes, adjusting for potential covariates such as age and IOP where applicable. Statistical significance was determined as a *P* value <0.05.

Results

Figure 2 illustrates the association between ΔV and the *invasive* measurement of OR using intravitreal injections in a cohort of 18 subjects. Of these 18 subjects, 7 were diagnosed with retinal vein occlusion, 5 had exudative age-related macular degeneration, 3 had diabetic macular edema, 2 had chronic central serous chorioretinopathy, and 1 had idiopathic choroidal neovascularization for which they were treated using bevacizumab. The clinical characteristics of these subjects are described in Table 1. The Spearman rank correlation between OR (measured invasively) and
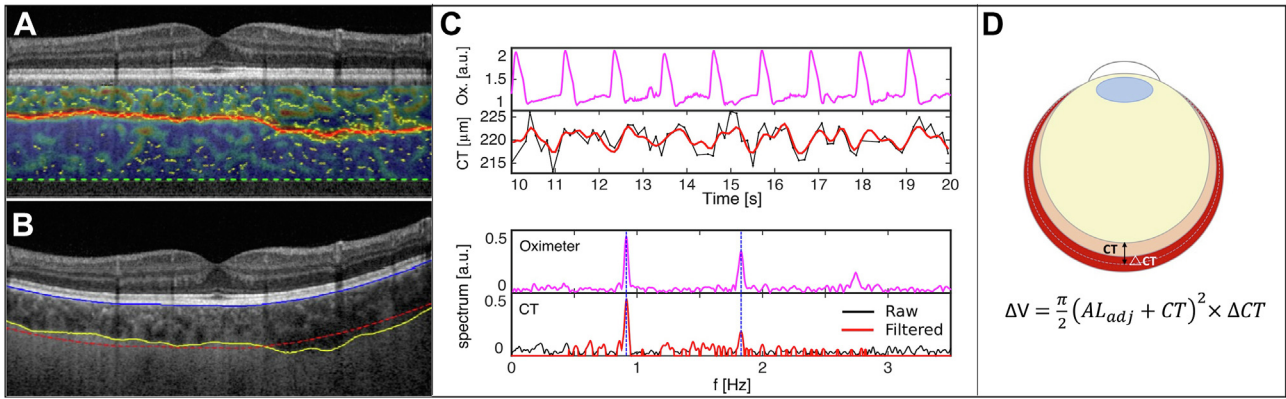
Figure 1. The ΔV is assessed using video-rate OCT imaging of the choroid. **A,** Analysis using a custom automated segmentation algorithm based on graph search with edge-probability weighting scheme is carried out. The heatmap shows node locations (yellow) and the choroid-sclera interface (red line). **B,** The original B-scan is overlaid with the retinal pigmented epithelium (blue), the choroid-sclera interface (yellow), and the mean choroidal thickness (CT) (red). **C,** Simultaneous measurement of the heart rate is used as validation. A frequency spectrum analysis of CT fluctuations in time is carried out, showing the oximeter signal, raw fluctuations of CT (black), and band-pass filtered CT signal (red). **D,** Finally, a 2-sphere model is used to estimate ΔV from the change in CT, where the dark red color represents choroidal filling during the cardiac cycle. AL = axial length; ΔCT = pulsatile choroidal thickness change; ΔV = pulsatile choroidal volume change.

ΔV (measured using dynamic OCT imaging) in the same eye is −0.664 ($P = 0.003$).

To further confirm this association in *noninvasive* measurements of OR, 217 eyes (199 subjects) were recruited. Their baseline characteristics are described in Table 2. Mean ΔV was 7.3 ± 3.4 μL for all 217 eyes, with a range of 3.0 to 20.8 μL. Figure 3 illustrates the distribution of ΔV in our cohort. The ΔV was 6.7 ± 2.9 μL in healthy eyes, 7.3 ± 3.4 μL in eyes with suspect discs, 7.2 ± 3.1 μL in glaucomatous eyes, and 8.6 ± 5.0 μL in eyes with OHT. Although ΔV values are higher in OHT eyes, the difference is not statistically significant ($P = 0.232$). A significant inverse correlation was found between ΔV and OR ($r_s = −0.748$, $P < 0.001$) in all eyes, as shown in Figure 4, such that eyes with lower ΔV

had higher OR. The inverse relationship between ΔV and OR was maintained in the different diagnostic groups ($P < 0.001$ for each): the Spearman rank correlation coefficient was −0.776 in healthy eyes; −0.744 in eyes with suspect discs; −0.681 in glaucomatous eyes; and −0.845 in eyes with OHT. No correlation was found between ΔV and age, blood pressure, IOP, or AL ($P \geq 0.05$).

Ocular rigidity was found to be correlated with IOP ($r_s = −0.181$, $P = 0.008$), ocular pulse amplitude (OPA) ($r_s = 0.429$, $P < 0.001$), and AL ($r_s = −0.335$, $P < 0.001$) but not with age and blood pressure in this cohort.

When comparing OR between glaucomatous (0.024 ± 0.012 μL^{-1}) and healthy eyes (0.028 ± 0.013 μL^{-1}), OR was found to be lower in eyes with glaucoma
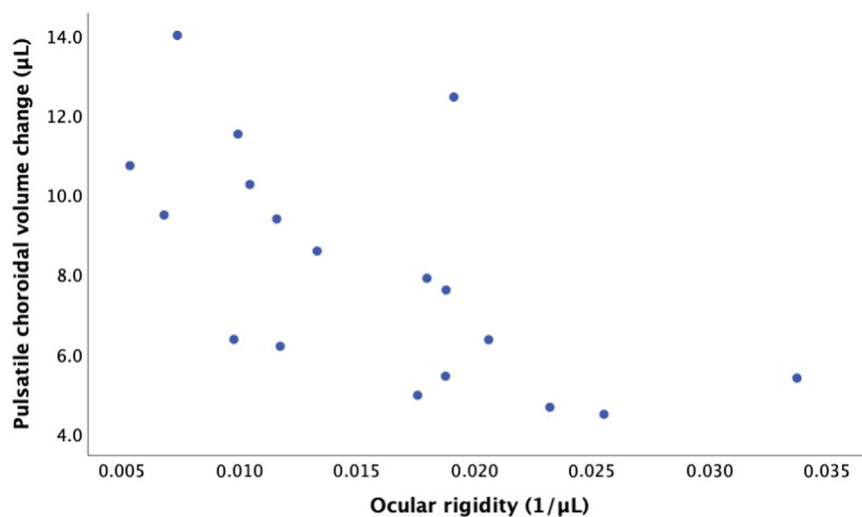
Figure 2. Scatterplot of the association between ocular rigidity coefficients (in μL^{-1}) obtained invasively and the pulsatile choroidal blood volume change obtained noninvasively (in μL) in a same eye in 18 subjects (blue circles) with retinal exudative diseases. The Spearman rank correlation coefficient between the ocular rigidity and the pulsatile choroidal blood volume change is −0.664 ($P = 0.003$).

Table 1. Demographic and Clinical Characteristics for 18 Eyes (18 Participants) with Exudative Retinal Diseases Who Underwent Noninvasive Measurement of the Pulsatile Choroidal Volume Change and Invasive Measurement of Ocular Rigidity

Eye (right)	7 (38.8%)
Sex (M)	10 (55.6%)
Ethnicity	
White	16 (88.9%)
African descent	1 (5.6%)
Other	1 (5.6%)
Diagnosis	
Retinal vein occlusion	7 (38.9%)
Diabetic macular edema	3 (16.7%)
Exudative age-related macular degeneration	5 (27.8%)
Chronic central serous chorioretinopathy	2 (11.1%)
Idiopathic juxtapapillary choroidal neovascularisation	1 (5.6%)
Age (yrs)	68 ± 10
Blood pressure (mm Hg)	
Systolic	145 ± 24
Diastolic	80 ± 8
Axial length (mm)	23.53 ± 0.90
DCT-IOP (mmHg)	20.0 ± 3.7
Ocular pulse amplitude (mmHg)	3.2 ± 0.7
Pulsatile choroidal volume change (μL)	8.1 ± 2.9
Ocular rigidity (μL^{-1})	0.022 ± 0.010

DCT = Dynamic Contour Tonometry; IOP = intraocular pressure.
The data are presented as mean ± standard deviation where applicable.

Table 2. Demographic and Clinical Characteristics for 217 Eyes from 199 Participants Who Underwent Noninvasive Measurements of Pulsatile Choroidal Volume Change and Ocular Rigidity

Eye (right)	122 (56.2%)
Sex (M)	92 (46.2%)
Ethnicity	
White	175 (87.9%)
African descent	17 (8.5%)
Other	7 (3.5%)
Diagnosis	
Healthy	74 (34.1%)
OHT	31 (14.3%)
Suspect discs	27 (12.4%)
POAG	85 (39.2%)
Age (yrs)	66 ± 14
Blood pressure (mmHg)	
Systolic	134 ± 19
Diastolic	78 ± 9
Axial length (mm)	24.29 ± 1.39
Maximum historic GAT-IOP (mmHg)	22 ± 7
GAT-IOP (mmHg)	17 ± 5
DCT-IOP (mmHg)	18.9 ± 4.3
Ocular pulse amplitude (mmHg)	3.1 ± 1.2
Pulsatile choroidal volume change (μL)	7.3 ± 3.4
Ocular rigidity (μL^{-1})	0.025 ± 0.013
Neuroretinal rim area (mm^2)	1.04 ± 0.29
RNFL thickness (μm)	
Average	81 ± 12
Range	49 to 107
Visual field mean deviation (dB)	
All groups	−1.98 ± 4.34
POAG only	−4.77 ± 5.89

DCT = Dynamic Contour Tonometry; GAT = Goldmann applanation tonometry; IOP = intraocular pressure; OHT = ocular hypertension; POAG = primary open-angle glaucoma; RNFL = retinal nerve fiber layer.
The data are presented as mean ± standard deviation where applicable.

($P = 0.026$). A tendency for higher ΔV was found in glaucomatous eyes, but it was not statistically significantly different compared to healthy eyes ($P = 0.266$).

Discussion

In this study, a strong inverse correlation was found between ΔV and OR, indicating an association between lower ΔV in more rigid eyes. The relationship with ΔV was consistent whether OR was obtained using an invasive procedure ($r_s = -0.664$, $P = 0.003$) or whether OR was obtained using the optical method ($r_s = -0.748$, $P < 0.001$). These correlations suggest an association between the biomechanics of the corneoscleral shell and ΔV. A possible interpretation of our results is that OR may influence choroidal filling. A more rigid eye may exert more resistance to tissue expansion and therefore limit the amount of pulsatile blood entering the choroid. Analogously, basic physiology links increased rigidity of blood vessels to reduced pulsatile volume.[14] The greater the stiffness of the artery wall, the smaller the pulse volume of blood in the arteries. This hypothesis would also be consistent with pathological processes documented elsewhere in the body, where reduced blood flow was found with increased arterial stiffness.[31,32] A previous report by our group showed a significant correlation between ΔV and OR in a smaller cohort (Sayah DN, et al IOVS 2016; 57: ARVO E-Abstract 3551). The inverse correlation between ΔV and OR was also predicted in a recent finite element

analysis of the ocular pulse,[13] but to our knowledge, this is the first time it has been validated clinically.

One could also propose that the pulse volume is influencing the OR rather than the reverse. Repetitive larger stretching of the sclera due to the pulse could stretch out the sclera, causing it to eventually become less rigid (unlike a single acute stretching of collagen, which causes it to become *more* rigid). We cannot reject this possibility, and it may be that both mechanisms are in play.

We also describe for the first time the distribution of ΔV in a large cohort composed of healthy eyes as well as eyes with POAG, suspect discs, and OHT. We report a mean ΔV of 7.3 ± 3.4 μL and a range of 3.0 to 20.8 μL. The axial resolution of our spectral domain-OCT imaging device limits the ability to measure ΔV values inferior to 3.0 μL (lower range of the distribution in Fig. 3), as may be encountered in eyes with very thin choroids, for example. Our graph of ΔV versus OR might have looked a little different if we had been able to measure these smaller ΔV. When considering only POAG versus healthy eyes, we found lower OR in glaucomatous eyes which is consistent with previous findings.[6–9] A more compliant eye (low OR) is associated with higher ΔV,
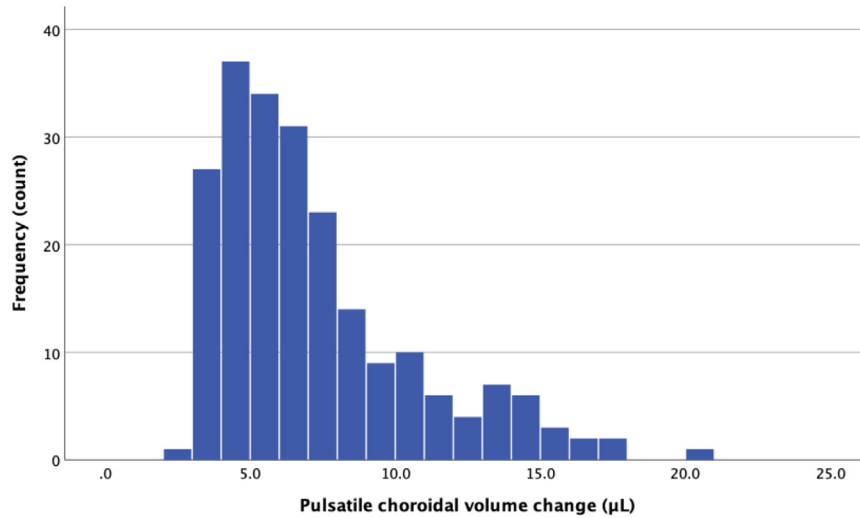
Figure 3. Histogram showing the distribution of the pulsatile choroidal volume change, or ΔV (in μL), in the cohort of 217 eyes (199 adult subjects). The ΔV was 6.7 ± 2.9 μL in the 74 healthy eyes, 7.3 ± 3.4 μL in the 27 eyes with suspect discs, 7.2 ± 3.1 μL in the 85 eyes with primary open-angle glaucoma, and 8.6 ± 5.0 μL in the 31 eyes with ocular hypertension. The overall mean pulsatile choroidal volume change was 7.3 ± 3.4 μL with a range of 3.0 to 20.8 μL. ΔV = pulsatile choroidal volume change.

and vice-versa. We could thus expect higher ΔV in eyes to be associated with more glaucomatous neuroretinal damage in this group in which eyes with early glaucoma damage predominate (average VF mean deviation was −4.77dB). A tendency for higher ΔV was found in eyes with glaucoma compared to healthy eyes; however, the difference was not statistically significant, indicating that factors other than ΔV (such as the pulsatile pressure change) also contribute to OR. This clinical study is the first to report on ΔV in glaucomatous and healthy eyes.

Several other factors are thought to be associated with ΔV and with OR, such as IOP, AL, and age. In our study,

OR was found to be correlated with IOP (r_s = −0.181, P = 0.008), OPA (r_s = 0.429, P < 0.001), and AL (r_s = −0.335, P < 0.001); however, no significant correlation was found between these variables and ΔV. Although a positive correlation is expected between IOP and OR due to the nonlinear behavior of the corneoscleral shell, we found a small negative correlation which has also been reported in previous clinical studies, suggesting a possible effect of IOP-lowering therapies on the association of OR and IOP.[7,8] Elongated eyes are usually associated with lower OR,[7,29,33] which is consistent with our findings. We could infer that longer eyes should be associated with
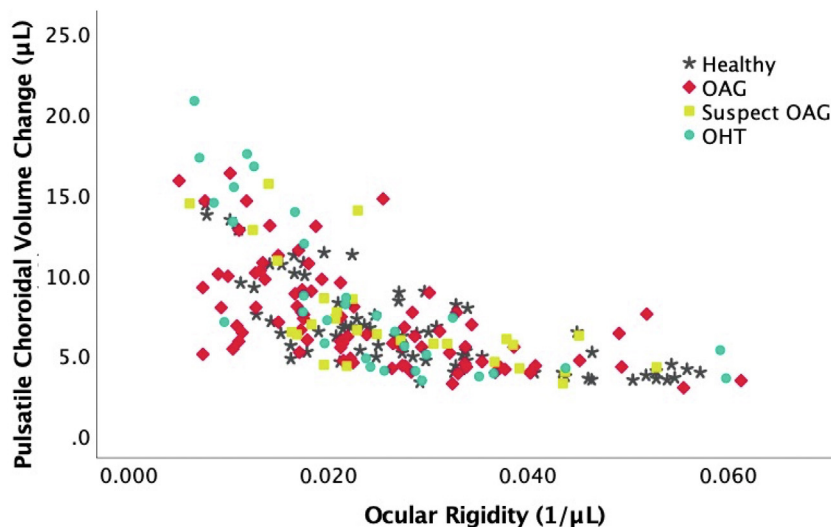
Figure 4. Scatterplot showing the relationship between the volume of pulsatile choroidal blood flow (ΔV) (in μL) and ocular rigidity (in μL⁻¹) in 217 eyes, including 74 healthy eyes (★), 85 eyes with primary open-angle glaucoma (◆), 27 eyes with suspect discs (■), and 31 eyes with ocular hypertension (●). The Spearman rank correlation coefficient for this relationship is −0.748 (P < 0.001). OAG = open-angle glaucoma; OHT = ocular hypertension.

higher ΔV; however, this correlation was not statistically significant in our cohort, possibly because the choroid tends to be thinner in high myopia.

We expect higher OR and a decreased ΔV in older subjects because tissue stiffening is thought to occur with aging.[6,7,29,34−36] We speculate that no significant correlation with age was found in this cohort due to the narrow age range of included participants.

The average ΔV obtained in this study is comparable with estimates of the pulsatile choroidal blood volume derived from known values for choroidal blood flow.[37] Alm et al reported choroidal blood flow of 677 mg/minute and retinal blood flow of 34 mg/minute in the Macaque eye, a ratio of 20:1.[37] Feke measured retinal blood flow of 80 μl/minute in the human retina.[38] Based on a ratio of 20:1, we might expect choroidal blood flow of 1600 μl/minute or 27 μl per heartbeat. The fraction of human choroidal blood flow that is pulsatile is around 12% in normals and 26% in elevated IOP as measured by laser Doppler flowmetry.[39] Thus, we might expect ΔV values in the range of 3 to 7 μl, which is close to our findings. Dastiridou et al [40] estimated the mean ocular pulse volume to be 6.03 μl at normal IOP using an invasive method. Because the choroid should account for 85% to 90% of this pulse, our measurements are also close to their estimates.

There are some limitations to this study. In the noninvasive group, the measurement of choroidal pulsatility was used to determine both ΔV and OR, because ΔV is one of the principal components of the Friedenwald Equation that we use to calculate OR. However, this limitation is remediated by showing a similar correlation between ΔV and OR (Fig. 2) in a cohort of patients in which the calculation of OR was determined *invasively*, independent of OCT.[30] In addition, OR is calculated from a pressure−volume relationship. As such, OR depends not only on the volume change (ΔV) but also on the pulsatile pressure change, ΔP. In the same cohort of 18 eyes in which OR was obtained invasively, the correlation between OR and the pulsatile pressure change, or OPA, was 0.418 ($P < 0.001$). Our data suggest that higher OR is associated with both lower pulsatile choroidal blood flow and higher OPA, as would be expected from basic tenets of biomechanics.

Two hundred thirty-five eyes from 217 subjects were included in this study. In other words, we used data from both eyes of 18 patients. Although intereye correlation may indicate that each data point does not represent an independent observation, this represents only a small fraction of our cohort, and the significance of the presented results is maintained when only 1 eye per subject is considered.

Another limitation of our study is that it measures only the *pulsatile* component of choroidal blood flow. *Total* choroidal blood flow would be a greater amount, but we cannot measure it with this technique. On the other hand, because pulsatile flow drives the mechanical expansion of ocular tissues, it may have great relevance when one tries to understand the interaction between blood flow and ocular mechanics.

Finally, OR is a global measure that accounts for the combined mechanical properties of the retina, choroid, and sclera. As such, it may not reflect local and heterogenous stiffness changes in specific areas of the eye such as the ONH region. The stiffness of the sclera is the main contributor to OR and was shown in silico to be the greatest factor to influence strain (deformation) at the ONH in glaucoma, perhaps more so than IOP.[4,5] Historically, the only direct method to measure OR is anterior chamber manometry, which involves intraoperative cannulation of the anterior chamber, preventing large-scale and longitudinal investigations of OR in living human eyes.[34,41−43] Noninvasive indirect methods based on differential tonometry were developed but were later deemed inaccurate.[44−49] Another technique based on choroidal laser Doppler flowmetry gave only relative values because choroidal blood flow was measured in arbitrary units.[7] The optical method used in the current study was first described by our group in 2015 [26] and is the only noninvasive and direct method for measuring ΔV and OR. The implication for this development is that we now can investigate the role of these parameters in healthy and diseased eyes.[8,22,30] We predict that ultimately this method could become a new clinical tool for diagnosing and predicting the progression of glaucomatous optic neuropathy and other diseases. Furthermore, coupling OR and ΔV with new methods to assess local deformation at the ONH [25] will lead to an enhanced understanding of glaucoma pathophysiology.

The results of this study suggest an association between the biomechanics of the corneoscleral shell and pulsatile ocular blood flow, which may indicate that a more rigid eye exerts more resistance to pulsatile choroidal expansion. This highlights the dynamic nature of both blood flow and biomechanics in the eye, as well as how they may interact, leading to a greater understanding of the pathophysiology of ocular disease.

Footnotes and Disclosures

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