Ocular Rigidity in Patients With Age-related Macular Degeneration

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● PURPOSE: To compare the ocular rigidity in vivo measurements of patients with age-related macular degeneration (AMD) and control subjects.

● DESIGN: Prospective comparative clinical study.

● METHODS: The pressure-volume relation and the ocular rigidity coefficient were compared among 32 patients with AMD (AMD group: 16 with neovascular and 16 with nonneovascular AMD) and 44 age-matched control patients (control group) who underwent operation for cataract. This was achieved by an injection of 200 µl of a balanced salt solution (in steps of 4.5 µl) through the limbus in the anterior chamber, while the intraocular pressure was monitored continually with a transducer, up to the limit of 30 mm Hg.

● RESULTS: The mean age (AMD group: 69.89 ± 15.92 years vs control group: 65.28 ± 12.34 years; $P = .195$), gender (AMD group: 13 female vs control group: 17 female; $P = .513$), eye's axial length (AMD group: 23.14 ± 0.75 mm vs control group: 23.04 ± 1.16 mm; $P = .725$) of patients with AMD and the healthy control subjects were comparable. No statistically significant difference in ocular rigidity measurements between patients with AMD and control subjects (AMD group: 0.0142 ± 0.0077 μl^{-1} vs control group: 0.0125 ± 0.0049 μl^{-1}; $P = .255$) was found. When we examined separately the two subgroups of patients with AMD (neovascular and nonneovascular AMD), the average ocular rigidity measurements were higher in patients with neovascular AMD vs both control subjects and patients with nonneovascular AMD (neovascular AMD group: 0.0186 ± 0.0078 μl^{-1} vs control group: 0.0125 ± 0.0048 μl^{-1} [$P = .014$] vs nonneovascular AMD group: 0.0104 ± 0.0053 μl^{-1} [$P = .004$]).

● CONCLUSIONS: Despite the limitations placed by the small sample of the examined cases, patients with neovascular AMD who are treated (with photodynamic therapy) have increased ocular rigidity measurements compared with patients with nonneovascular AMD and control patients. (Am J Ophthalmol 2006;141:611–615. © 2006 by Elsevier Inc. All rights reserved.)

A GE-RELATED MACULAR DEGENERATION (AMD) IS the leading cause of blindness in the developed world.[1–3] The cause of AMD is poorly understood, but it is most likely a complex disease in which several risk factors seem to have a potential role.[4] Genetic[5,6] and several other perspectives[4,7,8] (such as diet, smoking, elevated blood pressure, and history of cardiovascular diseases) are a few of the described risk factors that may contribute in the development of this disease. Furthermore, it has been hypothesized that ocular parameters (such as previous cataract extraction, iris color, refractive error, and choroidal blood flow) may also be involved in the development of AMD.[4,9,10] The implication of such a large number of possible etiologic factors indicates that we have not yet clarified the exact pathophysiologic mechanisms of this disease.

Ocular rigidity has been associated with several conditions such as aging,[11] osteogenesis imperfecta,[12] refractive error,[13] long-standing glaucoma,[14] scleral buckling,[15] vitrectomy, and intravitreal injection of a compressible gas.[16] Furthermore, the concept that ocular rigidity plays a role in the development of AMD has been described by Friedman and associates.[17] They found that patients with AMD had increased ocular rigidity measurements in comparison with control subjects. In that study, the calculation of scleral rigidity coefficient was performed indirectly (tonometry), although the authors did not distinguish the different forms of AMD. In our recent publication, we described an invasive, manometric in vivo measurement device of ocular rigidity.[11] Using this new measurement device of ocular rigidity in the present study, we compare the ocular rigidity in vivo measurements of patients with AMD and control subjects.

SUBJECTS AND METHODS

● SUBJECTS: The pressure-volume relation and the ocular rigidity coefficient were compared among 32 patients with AMD (AMD group: 16 with neovascular AMD and 16 with nonneovascular AMD) and 44 age-matched control patients (control group) who underwent operation for cataract. Pressure-volume relation was assessed by the injection of 200 μl of a balanced salt solution (in steps of 4.5 μl) through the limbus in the anterior chamber, while the associated intraocular pressure rise was monitored continuously with a transducer, up to the limit of 30 mm Hg. One eye of each patient was enrolled in the study. The necessary number of subjects who participated in the study was determined by an α-value of .05 and a β-value of .20 and an estimation for the variance of scleral rigidity value (K). The Institutional Review Board at the University of Crete approved the study protocol. All study procedures adhered to the Declaration of Helsinki for research that involves human subjects, and informed consent was obtained from each of the patients who participated in the study protocol.

A complete ocular examination was performed and included a measurement of visual acuity, slit lamp examination, measurement of intraocular pressure, indirect and direct ophthalmoscopy, and fundus photography. To minimize the possible effects of the changes in aqueous secretion and outflow (that might alter ocular rigidity measurements), subjects were excluded from the study if they had glaucoma or ocular hypertension, were eye drops users, or had had previous ophthalmic surgery (except photodynamic therapy for patients with neovascular AMD). The control group included patients who were examined for routine cataract extraction without evidence of AMD (early or late form).

Patients were classified as having AMD on the basis of standard findings by clinical examination and fluorescein angiography. AMD was graded as neovascular AMD (wet form) or nonneovascular AMD (dry form). Neovascular AMD included serous or hemorrhagic detachment of the retinal pigment epithelium (retinal pigment epithelium) or sensory retina; intraretinal, subretinal, sub–retinal pigment epithelium hemorrhages, or a combination; or subretinal fibrous scars. *Nonneovascular AMD* was defined as the presence of any of the following: areas of increased pigment or hypopigmentation associated with drusen or a central areola zone of RPE atrophy with visible choroidal vessels, in the absence of signs of neovascular AMD in the same eye. All patients with neovascular AMD had undergone treatment (photodynamic therapy) for their choroidal neovascularization. Lesions that were considered to be the result of generalized disease (such as diabetic retinopathy, chorioretinitis, high myopia, trauma, and congenital diseases) were excluded.

● MEASUREMENT SYSTEM: The ocular rigidity measurement device was described in our previous study[11] and
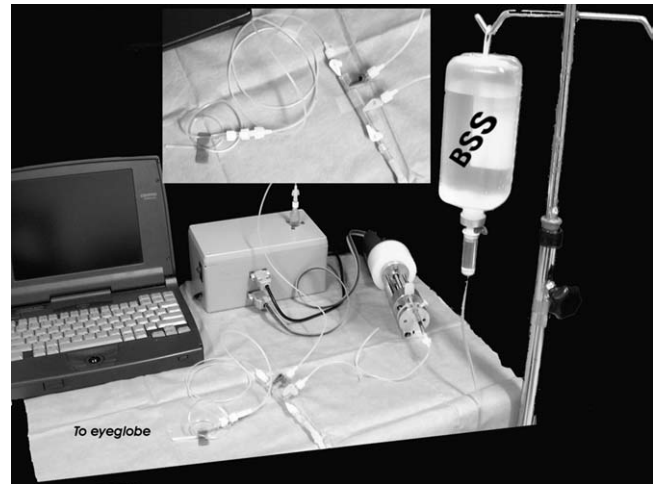

FIGURE 1. Ocular rigidity measurement device representation. The computer unit and transducer readout electronics, the mechanical dosage system (similar to an infusion pump), and the saline tubing manifold are distinguished. The circulation system is shown magnified in the upper part.

consists of three units: the computer unit and transducer readout electronics, the mechanical dosage system (similar to an infusion pump), and the saline tubing manifold (Figure 1).

A specifically designed computer program (developed in Microsoft Quick-Basic software [version 5.0; Microsoft Corporation, Redmond, Washington, USA]) is used for the control of the mechanical microdosage system and data acquisition from the pressure transducer. The pressure sensitivity of the system is 0.015 mm Hg. The dosage system has a volume resolution of 0.08 μl. The distribution system consists of polyethylene uncompressible extension tubules and a 22-guage intravenous needle. The pressure transducer was calibrated by sensing the pressure of a distilled water column. Before each experiment, the pressure transducer was tested with closed output to identify possible leaks in the tubule manifold.

All measurements were performed under retrobulbar anesthesia (1:1 lidocaine/bupivacaine mixture up to a total volume of 5 ml). The procedure usually started 15 minutes after retrobulbar injection. It was performed in a sterile field, and all components were gas sterilized.

After the insertion of the 22-gauge needle into the anterior chamber of the eye, the intraocular pressure was regulated to 10 mm Hg by appropriate irrigation or aspiration of BSS, and then the software waited until the system had reached equilibrium. The measurement initiates by the injecting steps of 4.5 μl of BSS. After each volume injection, the resultant intraocular pressure was measured twice, and the mean value was recorded, along with the corresponding value of the injected volume. The experiment proceeded until a final intraocular pressure of 30 mm Hg was reached or 200 μl of BSS were injected into the eye, whichever was achieved first. The system then

TABLE. Comparison of Age, Gender, and Axial Length of Patients With Age-related Macular Degeneration (AMD) and Healthy Control Subjects Whose Ocular Rigidity Was Measured

Characteristic	AMD Group	Control Subjects	P Value
Age (y)*	69.89 ± 15.92	65.28 ± 12.34	.195
Female (n)	13 (41%)	17 (39%)	.513
Axial length (mm)*	23.14 ± 0.75	23.04 ± 1.16	.725

*Data are given as mean ± SD.

FIGURE 2. Pressure (millimeters of Mercury)-volume (microliters) relation in patients with neovascular (n = 16) and nonneovascular age-related macular degeneration (n = 16) and in control subjects (n = 44).

regulated the intraocular pressure to 10 mm Hg, and the measurement was repeated.

All measurements were under continuous microscopic monitoring to avoid aqueous leakage from the cannulation site.

• DATA ANALYSIS: To acquire statistical power for our experiment at 0.80 with type II error β of .20 and ocular rigidity variance of 6.09×10^{-5}, we needed a sample size of at least 16 patients for each of the three groups (normal, neovascular, and nonneovascular). We have included 16 patients with neovascular AMD, 16 patients with nonneovascular AMD, and 44 normal patients. Results were expressed as mean ± SE (range) and mean (95% CI). The slope of the pressure-volume curves over the measurements was obtained for the pressure interval of 10 to 30 mm Hg with the use of linear regression analysis (least-square method).

Chi-square test was used to correlate ocular rigidity coefficient with the corresponding clinical dichotomous parameters (such as gender and the presence of AMD), and linear regression analysis was used to test the influence of continuous variables such as patient age and ocular axial length. For the examination of any significant differences between the mean values of rigidity coefficient for the AMD and control groups, unequal variances independent sample t test was used. To examine whether there were any differences between the two subgroups of the AMD group and control group, the nonparametric method of Kruskal-Wallis (because of a lack of homogeneity of variances) and the Mann-Whitney test was used appropriately. The level of significance was set at 5%.

RESULTS

THE MEAN AGE (AMD GROUP: 69.89 ± 15.92 YEARS VS CONtrol group: 65.28 ± 12.34 years; P = .195), gender (AMD group: 13 female [40.6%] vs control group: 17 female [38.6%]; P = .513), eye axial length (AMD group: 23.14 ± 0.75 mm vs control group: 23.04 ± 1.16 mm; P = .725) of patients with AMD and the healthy control subjects were comparable (Table).
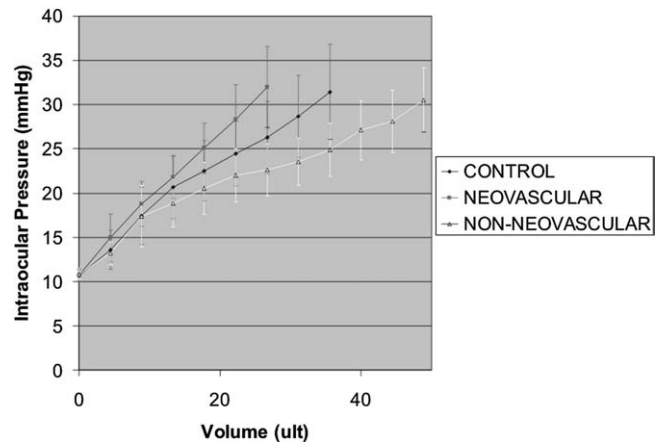
• PRESSURE/VOLUME MEASUREMENTS: None of the patients who were examined experienced any intra- or postoperative complications. The rigidity coefficient (K = dP/dV [mm Hg × μl^{-1}]) was calculated as the slope of the pressure vs volume curve for the examined intraocular pressure range (10 to 30 mm Hg). **In order to compare our values of ocular rigidity with the measurements of Friendewald we have divided the slope dP/dV by the factor 2.303*15.5 mm Hg in consistency to his calculations.**[13] Figure 2 shows the measurements of intraocular pressure vs injected volume of BSS into the eye for each group (control, neovascular, nonneovascular). Two consecutive measurements on the same eye were made, and the mean value ± SD is shown for each data point. Mean values were used for the calculation of the slope, which determined the ocular coefficient.

Figure 3 shows the box-plot graphs for each of the populations.

No statistically significant difference in ocular rigidity measurements between patients with AMD and control subjects (AMD group: 0.0142 ± 0.0077 μl^{-1} vs control group: 0.0125 ± 0.0049 μl^{-1}; P = .255, independent t test) was found. When we examined the two subgroups of patients with AMD (neovascular and nonneovascular) and the control group separately, a statistically significant difference among the three comparable groups was found (Kruskall-Wallis, P = .008). The average ocular rigidity measurements were higher in patients with neovascular AMD vs control subjects (neovascular AMD: 0.0186 ± 0.0078 μl^{-1} vs control group: 0.0125 ± 0.0048 μl^{-1}; P = .014, Mann-Whitney) and patients with nonneovascular AMD (neovascular AMD: 0.0186 ± 0.0078 μl^{-1} vs nonneovascular AMD: 0.0104 ± 0.0053 μl^{-1}; P = .004, Mann-Whitney), although similar findings were not found between control subjects and patients with nonneovascular AMD (control group: 0.0125 ± 0.0048 μl^{-1} vs non-
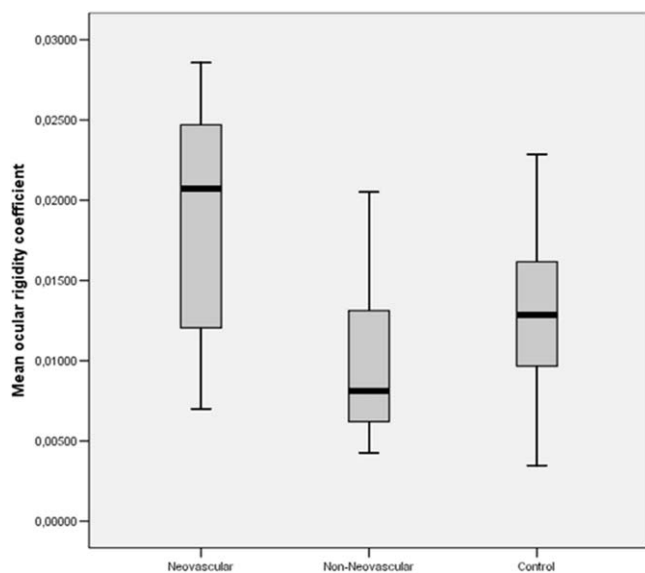
FIGURE 3. Mean ocular rigidity coefficient in patients with neovascular (n = 16) and nonneovascular age-related macular degeneration (n = 16) and in control subjects (n = 44).

neovascular AMD: 0.0104 ± 0.0053 μl^{-1}; $P = .130$, Mann-Whitney).

DISCUSSION

SEVERAL OCULAR PARAMETERS (SUCH AS CATARACT EX-traction, iris color, and refractive errors) in addition to smoking, atherosclerosis, and genetic factors have been described to be involved in the development of AMD.[4–10] In 1989, Friedman and associates[17] found that increased ocular rigidity may be a significant risk factor in the development of AMD. The possible pathophysiologic mechanism that has been proposed to explain this association is that the sclera in eyes with AMD becomes increasingly rigid and noncompliant, which increases the resistance of venous outflow and decreases the choroidal blood flow. This hypothesis is supported strongly by studies that have shown a positive correlation between the presence of decreased pulsatile ocular blood flow and pulse amplitude and the existence of exudative AMD.[18] Furthermore, using color Doppler imaging, Friedman and associates[19] found decreased velocity and increased pulsatility in ophthalmic arteries of patients with AMD and concluded that the blood velocities of the short posterior ciliary artery are lower in these patients.[20]

In our study, in contrast with study of Friedman and associates,[17] we did not find statistically significant differences between ocular rigidity measurements in control subjects and the total group of patients with AMD. However, we found a statistically significant increase in ocular rigidity measurements in patients with neovascular AMD in comparison with patients with the nonneovascu-

lar form and control subjects. These differences between the two studies could be explained by the differences in experimental methods (indirect-noninvasive vs direct-invasive manometric measurements) and the possibility of over representation of the neovascular form in the sample by Friedman and associates (they did not distinguish different AMD forms).

We did not find statistically significant differences in ocular rigidity measurements between patients with a nonneovascular form of AMD compared with age-matched control patients. Grunwald and associates[9] reported that the choroidal blood flow in the center of the fovea was lower in patients with nonexudative AMD than in age-matched control patients, measured by laser Doppler flowmetry. It is possible that choroidal blood flow in the center of the fovea may be decreased in these patients because of local factors that are independent of ocular rigidity. Furthermore, the differences in the ocular rigidity measurement coefficients between patients with nonneovascular and neovascular AMD may indicate that the underlying pathophysiologic mechanisms could be different in these two AMD groups.

Our findings support the theory of Friedman and associates[17] for AMD, at least for the neovascular form. According to this theory, the increasing ocular rigidity could lead to a decrease in the compliance of the sclera and the choroidal vessels. As the sclera becomes increasingly rigid and noncompliant, the filling of the vortex veins is decreased while the resistance of the choroidal vessels is being increased, which compromises Bruch's membrane (causing a Bruch's membrane defect at the macular area), with the final outcome of choroidal neovascularization (mechanical theory). Similarly, other well-studied AMD risk factors (such as atherosclerosis and systemic hypertension) may cause AMD through this pathophysiologic mechanism.

Another possible pathophysiologic process (in addition to the mechanical theory) by which the increasing ocular rigidity contributes to the development of choroidal neovascularization is the induced hypoxia (ishemic theory) that is caused by the decreased choroidal perfusion, which affects the normal function of retinal pigment epithelium. This hypoxia could lead to the secretion by the retinal pigment epithelium molecular angiogenic factors such as vascular endothelial growth factor, pigment epithelium–derived factor, and fibroblast growth factor[21,22] with the final outcome of choroidal neovascularization.

Several studies reported that axial length and age of the patients are risk factors for the development of AMD, although both of these parameters are correlated with ocular rigidity measurements.[11,23,24] Our study precludes a comparison of age of the patients and axial length between the examined study groups because these were matched parameters.

A few potential limitations are apparent in this study. The small sample of patients and the photodynamic

therapy that patients with neovascular AMD had undergone that might have affected the ocular rigidity measurements are the major limitations of the current study. Another important reservation is that we cannot determine whether the increased ocular rigidity in patients with neovascular AMD is a secondary effect or an independent primary pathogenic factor. It could be possible that the increased ocular rigidity measurements in patients with neovascular AMD are the results of the choroidal neovascularization and not the primary etiologic factor. Future prospective randomized studies, which will include more patients (with the use of a less invasive instrument to examine both eyes of patients with unilateral AMD) to elucidate the possible effect of photodynamic therapy, are needed to clarify these crucial limitations of the current study.

In summary, our study suggests that ocular rigidity is increased in patients with treated neovascular AMD in comparison with patients with nonneovascular AMD and control subjects. It seems that the increasing ocular rigidity could be an important component of the pathophysiologic cascade of neovascular AMD. It still remains to be elucidated whether hampered ocular rigidity is causative or reflects an event that results from the treatment or the changes that occur with aging and is accentuated in AMD. Further studies are needed to elucidate the possible correlation of ocular rigidity with AMD. If this correlation is further supported by additional studies (including more patients), it seems logical to develop treatment modalities that could alter ocular rigidity.

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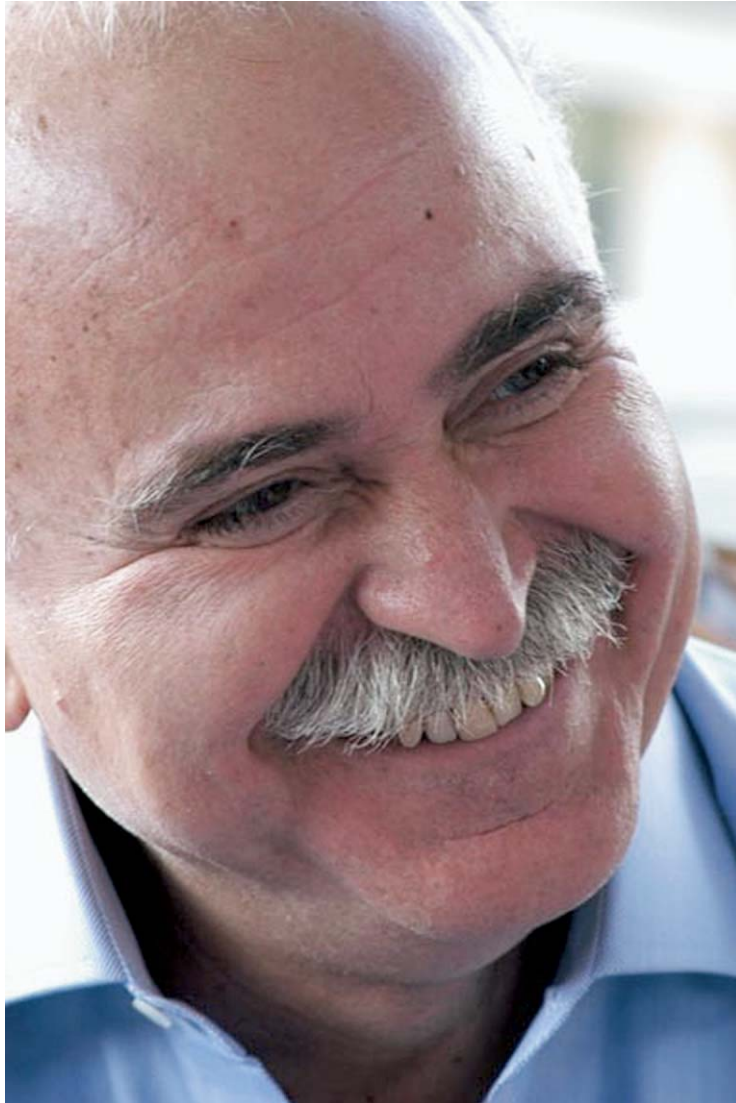
Biosketch

Ioannis G. Pallikaris, MD, PhD, was born in Chania, Crete, Greece. He graduated from the Medical School of Thessaloniki while he performed his doctoral thesis at the University of Zurich in 1981. Dr Pallikaris is the head of the Ophthalmic Department, Institute of Vision & Optics and Rector of the University of Crete. He has been honored with several awards such as "Barraquer", "Casebeer", "Kelman" and "Von Graefe". Currently, Dr Pallikaris is the Chairman of the Refractive Surgery Committee of ESCRS, a member of the Board of Directors of ISRS, and President of ESCRS

Biosketch

George Kymionis, MD, PhD, was born in Piraeus, Greece, in 1969. He graduated from the Medical School of University of Athens, and three years later he finished his PhD in the same university. He worked as a research fellow in Ophthalmology in Vardinoyiannion Eye Institute of Crete for several years, currently he is doing his residence in Ophthalmology in University Hospital of Crete. He participates in several research protocols and publications in medical journals, and he is a reviewer in several ophthalmic journals.