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Epidemiology of Vestibulo-Ocular Reflex Function: Data from the Baltimore Longitudinal Study of Aging

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Abstract

Objective—To determine age-related changes in vestibulo-ocular reflex (VOR) function in community-dwelling adults, and evaluate these for associations with demographic characteristics and cardiovascular risk factors.

Study Design—Cross-sectional analysis within the Baltimore Longitudinal Study of Aging (BLSA), a longitudinal prospective cohort study.

Setting—Vestibular testing laboratory within an acute care teaching hospital.

Patients—Community-dwelling adults enrolled in the BLSA.

Intervention(s)—Horizontal VOR gain measurement using video head-impulse testing and visual acuity testing.

Main Outcome Measure(s)—VOR gain was calculated as the ratio of eye velocity to head velocity. Demographic and cardiovascular risk factor data were collected through study questionnaires.

Results—One hundred nine subjects were analyzed with mean age (SD) 69.9 years (14.2), with a range from 26 to 92 years. VOR gain remained stable from age 26 to 79 after which it significantly declined at a rate of 0.012/year ($p = 0.033$) in adjusted analyses. Individuals aged 80 years or older had a nearly 8-fold increased odds of VOR gain less than 0.80 relative to those aged less than 80 years in multivariate models (prevalence of 13.2% vs. 2.8%; OR 7.79, 95% CI: 1.04–58.38). Otherwise, VOR gain did not differ significantly across demographic or cardiovascular risk groups.

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The authors disclose no conflicts of interest.

Conclusion—We report age-related decline in VOR function in individuals aged 80 years and older. Further analyses are in progress to establish the significance of these VOR abnormalities to functional and mobility outcomes in older individuals.

Keywords

Aging; Head-impulse test; Vestibular dysfunction; Vestibulo-ocular reflex

The vestibular system senses head movement and spatial orientation and produces reflexes to stabilize gaze and maintain posture. Epidemiologic analyses of vestibular dysfunction were recently conducted using data from the National Health and Nutrition Examination Survey (NHANES). The study estimated vestibular function in over 5,000 U.S. adults aged 40 or older based on the ability to maintain balance on a foam-padded surface with eyes closed for 30 seconds. Thirty-five percent of adults were unable to maintain balance on this test, and inability to complete this test was significantly associated with increased fall risk (1). Moreover, the odds of balance impairment increased significantly with age and with a history of diabetes mellitus (1).

Postural tests are limited in their ability to specifically measure vestibular function, given that performance on these tests also reflects other sensory inputs, central processes, and motor function. The head-impulse test (HIT) is a more specific clinical test of the peripheral vestibular system that measures the function of the vestibulo-ocular reflex (VOR) (2). A recent pilot study administered the HIT in a cohort of 50 healthy older adults to evaluate the prevalence of age-related vestibular loss in the community. The study observed a 50% prevalence of HIT abnormality, which was significantly associated with slow gait speed and fall risk (3).

In this study, we sought to confirm and extend the findings of the pilot study by quantitatively evaluating VOR function in a larger cohort of community-dwelling individuals across the age range from 26 to 92 years. We performed video head-impulse testing (vHIT) and evaluated changes in VOR gain in a group of participants of the Baltimore Longitudinal Study of Aging (BLSA) dispersed over a wide age range. The large and diverse BLSA cohort also allowed us to assess whether other demographic characteristics and cardiovascular risk factors are independent correlates of VOR function.

This observational epidemiological study provides an estimate of the magnitude of age-related vestibular loss in community-dwelling older individuals and its distribution in the U.S. population.

MATERIALS AND METHODS

Subjects

The BLSA is an ongoing prospective cohort study initiated by the National Institute on Aging (NIA) in 1958. Subjects consist of community-dwelling participants who travel to the NIA every 1 to 4 years for 2.5 days of testing. Subjects under age 60 are assessed every 4 years, subjects aged 60 to 79 years are assessed every 2 years, and subjects age 80 and older are assessed every year. With respect to vHIT, individuals were excluded if they could not

participate in the testing protocol because of blindness, poor neck range of motion, cervical spine instability, or history of vascular surgery in the neck. From February to December 2013, 314 participants were evaluated at the BLSA, of whom 167 (53%) completed vHIT testing. Of the participants who did not undergo testing, 115 were not tested because of time constraints and/or tester unavailability, 18 were ineligible according to exclusion criteria, and 14 were unable to complete testing because of technical difficulties, such as imprecise pupil tracking. Tested versus untested participants did not differ significantly by age, sex, race, or cardiovascular risk factors. Demographic data (age, sex, and race/ethnicity), cardiovascular risk factor data (history of hypertension, diabetes mellitus, and hyperlipidemia), and smoking history were collected from extensive interviews. Participants were asked to designate a race from the following options: White, Black or African Americans, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, “Two or More Races,” “Don’t Know,” and “Refused.” History of hypertension was assessed with the question, “Has a doctor or other health profession ever said you had high blood pressure or hypertension?” History of diabetes mellitus was assessed with the question, “Has a doctor or other health professional ever said you had diabetes, glucose intolerance, or high blood sugar?” History of hyperlipidemia was assessed with the question, “Has a doctor or other health professional ever said you had high cholesterol triglycerides, dyslipidemia, or hypercholesterolemia?” History of smoking was assessed by asking participants “Have you smoked at least 100 cigarettes over your entire life,” “Have you smoked at least 50 cigars over your entire life,” and “Have you smoked at least 3 packages of pipe tobacco over your entire life?” All participants provided written informed consent, and the BLSA study protocol was approved by the local institutional review board.

Quantitative Head-Impulse Testing

The ICS Impulse 3-D video head-impulse test (vHIT) system (GN Otometrics, Schaumburg, IL, USA) was used per published specifications (4,5). The vHIT system consists of a high-speed digital video camera, a mirror to reflect the eye to the camera, and an inertial measurement unit, all mounted to a lightweight glasses frame. Because individuals have been shown to adapt their VOR gain according to the rotational magnification induced by habitual use of corrective spectacles (i.e., glasses) (6,7), subjects were instructed to remove corrective spectacles for a minimum duration of 5 minutes before testing. The right eye was illuminated by two infrared light-emitting diodes and eye position was calibrated with projected targets from a glasses-mounted laser. Subjects were instructed to fixate on a stationary target projected 124 cm ahead at eye level. Approximately 10 horizontal head impulses to each side were manually applied with unpredictable direction and timing. Peak head velocity ranged typically from 150 to 200 degrees per second. The right eye position was recorded at 250 Hz and velocity was acquired from a two-point differentiator and was low-pass filtered (0–30 Hz bandwidth). Recordings in which the eye movement appeared to precede the head movement have been shown to represent goggle slippage. When this pattern was observed during vHIT testing, attempts were made to improve goggle fit, including tightening the goggle frame and trying to vary the position of the goggles on the orbital rim. Studies suggest that some individuals are not good candidates for vHIT, perhaps due to anatomic features of the face or eye (8). Indeed, despite efforts to improve goggle fit, a subset of participants had persistent traces where the eye appeared to move before the

head. Before any statistical analysis was performed, two authors (C.L. and Y.A.) reviewed eye- and head-velocity data for each tested participant and identified 58 participants who had evidence of goggle slippage and were not considered for further analysis. Interestingly, these 58 participants were significantly older than the included study sample (69.9 ± 14.3 vs. 76.3 ± 9.8 years, $p = 0.003$). These 58 participants also contained a higher proportion of females compared to the study sample (65% vs. 47%, $p = 0.021$). In the remaining 109 participants, horizontal VOR gain, defined as the ratio of the area under the desaccaded eye movement curve to the area under the head movement curve (i.e., a position gain), was calculated. There was a high correlation between left and right sides ($r = 0.76$, $p < 0.0001$); as such, VOR gains from each side were averaged to obtain one value for each individual.

A normal, compensatory VOR gain should equal 1.0. Loss of peripheral vestibular function typically manifests as decreased VOR gains, with accompanying covert and/or overt saccades to restore visual fixation (9). However, we recently observed superunity (greater than 1.0) gain values in several older subjects with both search coil and VOG testing systems (10). In our cohort of 109 individuals with evaluable vHIT traces, VOR gains as high as 1.18 were observed. To explore potential contributors to the superunity gains, we conducted several sub-analyses detailed below.

Effect of Static Visual Acuity on VOR Function

Adequate visual acuity is required to fixate the far target during vHIT. Subjects were only eligible for vHIT testing if they were able to clearly visualize the target. Nevertheless, we evaluated the association between static visual acuity and vHIT gain to see if elevated VOR gains could be a result of poor visual acuity. Static visual acuity was measured in a separate session with the CVS-1000 HGT ETDRS acuity chart (VectorVision, Greenville, OH, USA).

Association Between Spectacle Correction and VOR Gain

We investigated whether superunity gains may be a result of the use of magnifying spectacles for presbyopia, a common condition in the elderly. Increased gains associated with magnifying spectacles have been observed previously for low-frequency VOR testing (6,7). Given that we could not perform ancillary testing within the BLSA, we recruited five older individuals from our pilot study (3) who habitually wore magnifying lenses. We used the EyeSeeCam VOG system (Interacoustics, Eden Prairie, MN, USA) per published specifications (10,11). We measured their VOR gain at baseline and assessed if their VOR gain was a function of the amount of spectacle correction. We then measured VOR gain at repeated intervals over a 1-hour session during which subjects performed ×1 gaze stabilization exercises in between measurements. We examined whether the participants could “de-adapt” their VOR gain (i.e., experience a change in VOR gain towards 1.0) after spectacle removal.

Analysis

VOR gain values were evaluated across the entire population and stratified by demographic and cardiovascular characteristics. We considered several methods of analyzing VOR gain, including VOR gain as a continuous variable and VOR gain dichotomized into normal and

abnormal based on various cutoff thresholds. We tested linear splines to explore non-linear relationships between VOR gain and age. Multiple linear regression was used to analyze continuous outcome measures, and multiple logistic regression was used for categorical outcomes. All analyses were carried out in Stata Data Analysis and Statistical software (College Station, TX, USA). A p value less than 0.05 was considered statistically significant.

To evaluate the association between spectacle correction and VOR gain, lens prescriptions were used to calculate effective corrective power in the horizontal meridian, $D_{horiz} = D_{sph} + D_{axis}\cos(\phi)$, where D_{sph} is the sphere lens power, D_{axis} is the cylinder lens power, and ϕ is the axis of the cylinder relative to the horizontal plane (6). We then evaluated the relationship between VOR gain and effective corrective power and observed for changes in VOR gain over time.

RESULTS

Of the 109 subjects who had evaluable vHIT data, the mean age (SD) was 69.9 years (14.2), with a range from 26 to 92 years. Forty-seven percent of subjects were female, 22% were African American, 37% had hypertension, 20% had diabetes mellitus, 71% had hyperlipidemia, and 38% had a positive smoking history (Table 1). We first evaluated the distribution of VOR gain (as a continuous variable) as a function of age. Simple linear regression showed that VOR gain declines by 0.002/year overall ($p = 0.013$). To evaluate for non-linearities in the age-VOR association, we generated locally weighted scatterplot smoothing plots of the data. We observed a non-linear relationship between VOR gain and age, with a change in the association ("knot") at age 80. Therefore, we performed linear spline regression with one knot at 80 years. We observed that VOR gain remained stable from age 26 to 79 after which it significantly declined at a rate of 0.016/year ($p = 0.001$) in bivariate analysis (Fig. 1). After adjusting for sex, race, hypertension, diabetes mellitus, hyperlipidemia, and smoking history, these findings were substantially confirmed, although the estimated average rate of age-associated decline was less steep (0.012/year; $p = 0.033$).

Of the 109 subjects, 49 had VOR gain values above 1.0 (i.e., "superunity" gains). We evaluated whether these superunity gains could be attributed to technical or measurement error associated with use of the vHIT system in older individuals. First, we considered whether gain measurement could be influenced by visual acuity and the ability to see the target clearly. We did not observe a significant association between VOR gain and static visual acuity in our study ($\beta = -0.070$; $p = 0.376$) (Fig. 2).

We also investigated whether superunity gains may be a result of the use of magnifying spectacles for presbyopia. In our sample of five subjects (described above), three exhibited superunity VOR gains. Moreover, VOR gain seemed to be a function of spectacle magnification, whereby the habitual use of magnifying spectacles may lead to adaptation of VOR gain to values greater than 1.0 (Fig. 3). We did not observe evidence of "de-adaptation," manifest as a change in VOR gain towards 1.0 over 1 hour after spectacle removal. These data suggest that the use of magnifying lenses may contribute to the superunity gains in this study.

We next evaluated for differences in VOR gain by demographic and cardiovascular characteristics. In bivariate analyses, we observed that females had significantly higher VOR gains ($p = 0.029$) (Table 1). VOR gain did not differ significantly across sex, race/ethnicity, or cardiovascular risk factors. In multivariate analyses, with the exception of age, VOR gain did not differ significantly across demographic or cardiovascular risk groups (Table 2).

We further created dichotomous categories of VOR gain and evaluated the odds of having a low VOR gain (vs. high) associated with demographic and cardiovascular characteristics (Table 3). In our well-functioning BLSA population, seven (6.4%) individuals exhibited VOR gains less than 0.80. Individuals aged 80 years or older had a nearly 8-fold increased odds of VOR gain less than 0.80 relative to those aged less than 80 years in multivariate models (prevalence of 13.2% vs. 2.8%; OR 7.79, 95% CI: 1.04–58.38). No other demographic or cardiovascular risk factors were significantly associated with having a low VOR gain of less than 0.80.

DISCUSSION

The central finding of this study is that VOR function remained stable up to age 80, after which it decreased significantly with age. These findings were established using a highly specific test of VOR function, the vHIT, and in a large, diverse, and rigorously studied cohort of community-dwelling adults. These findings add to the body of literature that has studied age-related effects on the VOR (12–17). Peterka et al. reported decreased VOR gain to sinusoidal rotation with age, along with increased postural sway (18). In patients aged 18 to 89, Paige et al. demonstrated age-related changes in phase measures and declining VOR responses in response to high-amplitude and high-velocity sinusoidal rotations (19). A 5-year longitudinal study of vestibular function observed a significant decrease in VOR gain to sinusoidal stimuli, specific to higher velocities (12). The mean age on entry of the participants in this longitudinal study was 78.5 years; therefore, the VOR gain declines may have been driven by the preponderance of oldest old participants in that study. Our findings are also consistent with histopathologic reports showing significant age-related declines in vestibular sensory hair cell populations in human temporal bones (20–22) as well as age-related neuronal loss in the human vestibular nucleus complex (23).

It has been shown that specific vestibular structures differentially degenerate with age. Although sensory hair cell counts decrease by 6% per decade starting from birth (21,24,25), primary vestibular afferent fibers tend to degenerate from middle age on, with 35% of afferents remaining in individuals age 70 to 85 years (24,26). Further histopathologic studies show that cells in Scarpa’s ganglion decline starting at age 30 with a steep decrease after age 60 (25,27,28) whereas vestibular nuclei neurons decrease by 3% per decade between 40 and 90 years of age (23,29). It has been demonstrated that increased sensitivities of afferent nerve fibers and central mechanisms can compensate for earlier-onset hair cell loss, thus maintaining normal function until more significant levels of degeneration occur at older ages (30). Our findings of impaired VOR performance beginning at age 80 is consistent with the evidence that the vestibular degeneration observed histopathologically may be clinically manifest only in the oldest old.

In this study, we also report a significant number of superunity gains, for which we propose several theories. Increased gains may represent disinhibition or “decalibration” of the VOR associated with cerebellar degeneration (31). Additionally, increased gain variability, and specifically superunity gains, could be a result of the habitual use of magnifying spectacles for presbyopia (6,7), which is a nearly ubiquitous condition in the elderly. Indeed, in our ancillary sample of five individuals who habitually wore magnifying lenses, we observed a positive relationship between diopter lens correction and VOR gain. Whether this upward calibration of VOR gain represents a helpful versus harmful adaptation or whether this depends on the context remains to be further investigated. Further technical reasons for observing increasing gain variability with age are discussed below.

In addition to age-related changes in VOR function, this study examined the influence of other demographic factors. In unadjusted analyses, females had significantly higher mean VOR gains and this trend persisted after multivariate adjustment. Only a few studies have reported on sex-related differences in vestibular function. Three-dimensional measurements of the human vestibular apparatus have shown that males tend to have larger diameter semicircular canals as well as larger surface areas of the utricular and saccular maculae (32). However, the functional significance of the sex differences in VOR found in this study is unclear. Cervical vestibular evoked myogenic potential testing in a population of young adults showed no sex differences in response latency or amplitude (33). Future studies will be needed to more firmly establish any sex differences in vestibular function, as they are clearly known to exist for auditory function.

Cardiovascular risk factors had no association with VOR function in the study population. Previous analyses from NHANES demonstrated a significantly higher prevalence of balance dysfunction associated with tobacco use greater than or equal to 20 pack-years, hypertension, and diabetes (1). Discrepancies between these two studies may be attributed to the fact that cardiovascular risk factors may play a greater role in global measures of balance function (used in NHANES) versus the specific measure of vestibular function used in this study. Moreover, participants in the BLSA appear to be healthier and have less burden of cardiovascular disease compared to participants in NHANES. NHANES randomly surveys non-institutionalized households across the United States, whereas participants in the BLSA undergo a more rigorous screening process, selecting for individuals who encounter no difficulties in performing activities of daily living, are able to walk independently for at least 400 m, and have no history of cardiovascular disease or diabetes at the time of enrollment. Although 25.4% of the NHANES study population reported a greater than or equal to 20 pack-year history of smoking, our study population averaged 3.2 pack-years, with a maximum reported smoking history of 9 pack-years. Furthermore, the NHANES study defined hypertension and diabetes based on physician diagnosis and/or physical examination, whereas our study utilized a medical interview inquiring about high blood pressure, diabetes, glucose intolerance, and high cholesterol/triglycerides.

Several limitations of this study should be noted. As mentioned previously, participants in the BLSA are subject to a rigorous screening process and represent a population of healthy, well-functioning adults compared to the U.S. population. As such, our findings of VOR gain trajectories with age may apply to ideal aging but may not be applicable to other

populations. We also note important strengths and limitations of quantitative HIT using video-based systems. vHIT is spurring a revolution in vestibular testing by bringing quantitative VOR gain measurement to the bedside and clinical setting. Several studies (4,5,34) have demonstrated the validity of vHIT compared to the gold standard of search coils, with one recent study focused on older individuals (10). However, certain technical limitations should be noted. Approximately one third of participants had vHIT recordings that were not evaluable. These participants were older and more likely to be female than participants with evaluable traces. Excess skin laxity or the presence of a large amount of hair under the goggle strap contribute to goggle slippage and may contribute to the higher number of unevaluable traces in older females. One study demonstrated that the goggle slippage artifact could be reduced by applying a dental paste cast to stabilize the goggle frame on the bridge of the subject's nose (8). We chose not to use this technique because of the difficulty in standardizing this procedure across our cohort. Refinements in vHIT goggle materials and goggle fit, as well as the development of non–goggle-based vHIT systems, will likely improve the proportion of evaluable recordings in the future. Additional technical limitations of the vHIT are that eyelid laxity and pupil abnormalities as a result of cataract surgery may interfere with the vHIT pupil tracking software. Moreover, interocular differences in VOR gain have been reported in which gains of the adducting eye consistently exceeded gains of the abducting eye by an average of 15.3% (35). Therefore, for accurate measurements, binocular recording is recommended. Because of the design of the ICS Impulse vHIT goggles, only the right eye was used to measure VOR gain in our study. Again, further refinements in the vHIT systems including more robust pupil tracking algorithms and the ability to record binocularly are being developed and will improve vHIT testing in the future.

In this study, we observed distinctive age-related decline in VOR function in individuals age 80 years and older. Studies are ongoing which are aimed at clarifying the functional consequences of such vestibular impairment in older persons.

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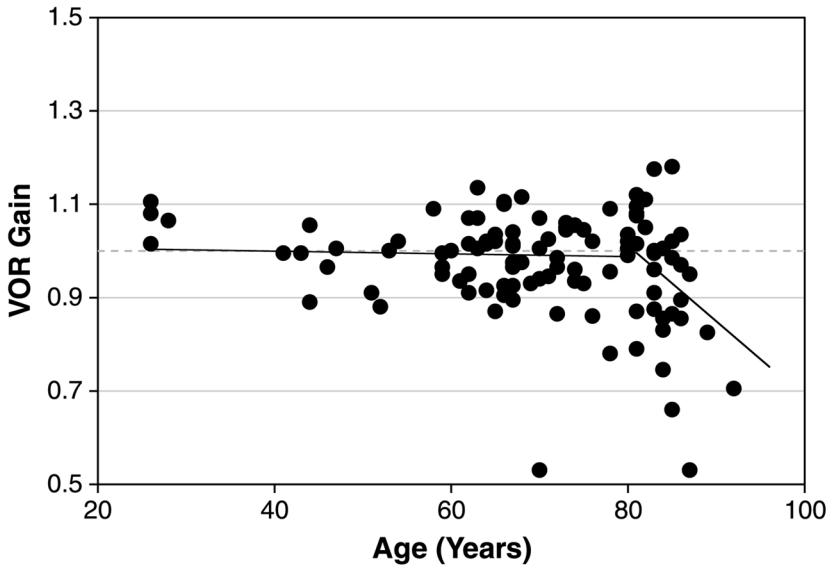

FIG. 1.

VOR gain in the overall study population. *Dotted gray line* shows reference of VOR gain = 1.0.

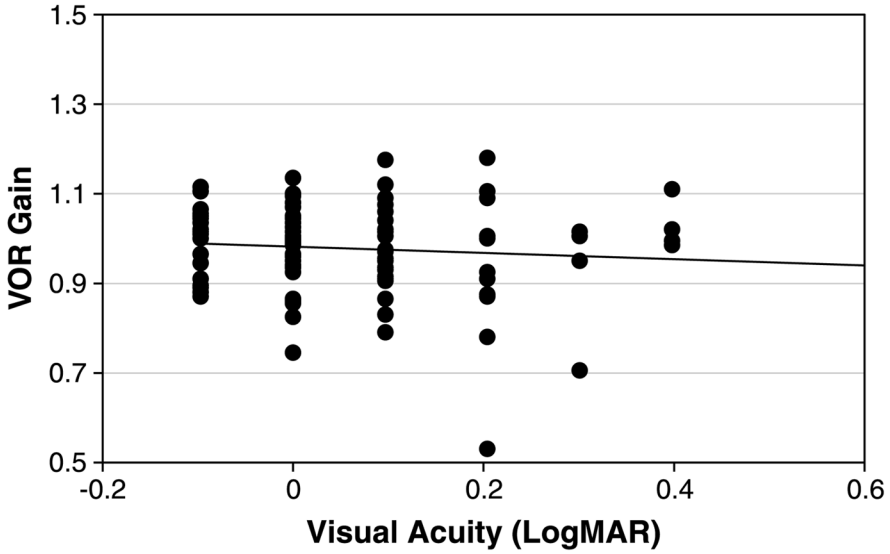

FIG. 2.
VOR gain and static visual acuity.

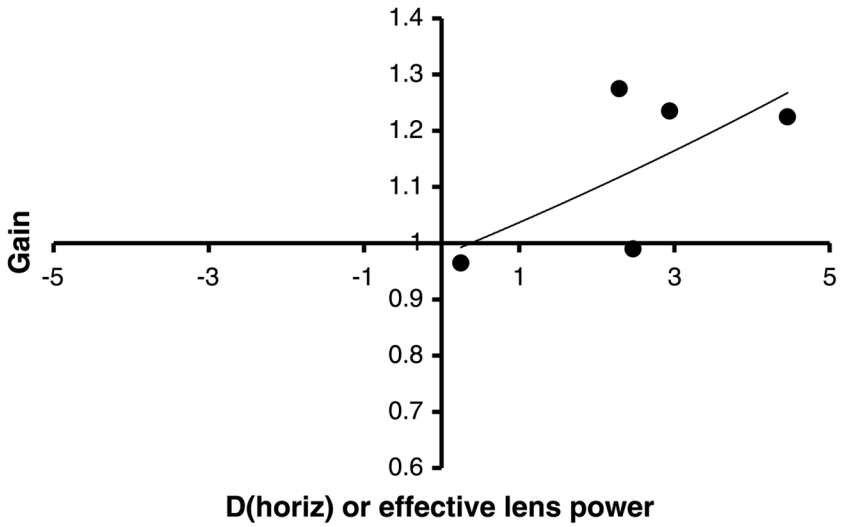

FIG. 3.
Variation of VOR gain with lens power.

TABLE 1

VOR gain stratified by demographic and cardiovascular risk characteristics in BLSA 2013

	No. (%)of participants	Mean VOR gain (SD)	*p*
Demographic characteristics			
Age	109	0.97 (0.11)	0.013
Sex			0.029
Male	58 (53.2)	0.95 (0.11)	
Female	51 (46.8)	1.00 (0.11)	
Race/ethnicity			0.109[a]
Caucasian	73 (68.9)	0.96 (0.12)	
African American	23 (21.7)	1.00 (0.08)	
Other	1 (1.0)	1.02 (0.00)	
Unknown	9 (8.5)	0.98 (0.10)	
Cardiovascular risk factors			
Hypertension			0.123
Yes	39 (37.1)	0.99 (0.09)	
No	66 (62.9)	0.96 (0.12)	
Diabetes mellitus			0.118
Yes	21 (20.0)	1.00 (0.07)	
No	84 (80.0)	0.96 (0.12)	
Hyperlipidemia			0.447
Yes	75 (71.4)	0.97 (0.12)	
No	30 (28.6)	0.98 (0.08)	
Smoking history			0.707
Yes	39 (37.5)	0.98 (0.09)	
No	65 (62.5)	0.97 (0.12)	

[a]Because only one individual reported a race other than Caucasian or African American, he/she was excluded from the race analysis.

TABLE 2

Multiple regression analysis of VOR gain with demographic and cardiovascular risk factors

Characteristics	VOR gain	
	β	*p*
Age <80	−0.001	0.513
Age ≥80	−0.012	0.033
Sex	−0.037	0.115
Race	0.012	0.668
Hypertension	0.047	0.063
Diabetes mellitus	0.014	0.668
Hyperlipidemia	−0.028	0.251
Smoking history	−0.003	0.908

TABLE 3

Adjusted odds ratio of lower VOR gain cutoff by age

Age group	Gain <0.80	
	Prevalence N (%)	OR (95% CI)
<80	2 (2.8)	1.00[a]
80+	5 (13.2)	7.79 (1.04–58.38)

[a] Analysis adjusted for sex, hypertension, and smoking history only as all individuals ≥80 with VOR gain <0.80 were Caucasian and negative for diabetes mellitus.