Glaucoma is a leading cause of vision-related morbidity worldwide.1–4 The number of people with glaucoma is estimated to increase to 111.8 million in 2040 owing to the global trend toward an aging society.5 An important feature of glaucoma is its long asymptomatic period. The irreversibility and social burden of glaucomatous damage emphasize strongly the importance of early detection before significant field loss has developed.6,7 However, the detection of glaucoma is presently often incidental because population-based screening for open-angle glaucoma (OAG) is not recommended.8

Although IOP is the most important and the only modifiable risk factor for glaucoma,9–13 not all patients with glaucoma show elevated IOP. Cumulative evidence suggests that vascular pathology also plays a role in OAG. Several studies have reported associations between glaucoma and systemic vascular diseases including hypertension,14 diabetic mellitus,15 migraine,16,17 vasospasm,18 and nocturnal hypotension.19 Local vascular factors, including optic disc hemorrhage,20–22 peripapillary atrophy,23 and reduced blood flow to the optic nerve head (OHN)24 were also reported to be associated with development or progression of glaucoma.

Furthermore, a number of studies have found that retinal vessel diameter (RVD) may be associated with glaucoma pathogenesis. The narrowing of retinal arteriolar diameter was shown in glaucoma patients.25–28 A recent study suggested that such vascular change might result from thinning of the retinal nerve fiber layer (RNFL),29 whereas the Blue Mountains Eye Study30 demonstrated that retinal arteriolar narrowing could be a risk factor for development of OAG. Previously, our group revealed that retinal arteriolar diameter has a positive correlation with RNFL thickness in glaucoma patients,25 and others also reported the association between RVD and glaucoma severity assessed by vertical cup-to-disc ratio,28 neuroretinal rim area, or visual field (VF) indices.31 Although it still remains unclear whether alterations in RVD precede or follow glaucomatous changes of the ONH, the aforementioned findings suggest that RVD changes are associated with the development or progression of glaucoma.

On the basis of these observations, we hypothesized that RVD may serve as a biomarker indicating the level of glaucomatous damage. To date, there have been a few attempts to investigate the diagnostic ability of RVD measurements in detection of glaucoma. This study was designed to assess the diagnostic capability of the RVD indices in OAG, and compare it with that of peripapillary RNFL thickness measured using optical coherence tomography (OCT). In addition, we evaluated the diagnostic performances between eyes with high-tension glaucoma (HTG) and those with low-

**Glaucoma**

**Diagnostic Ability of Retinal Vessel Diameter Measurements in Open-Angle Glaucoma**

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**PURPOSE.** To determine the diagnostic ability of retinal vessel diameter (RVD) measurements and the factors related to retinal vascular diameters in patients with open-angle glaucoma (OAG).

**METHODS.** This retrospective observational study included 145 patients with OAG (63 with high-tension and 82 with low-tension glaucoma) and 60 healthy controls. The central retinal arteriolar equivalent (CRAE) and central retinal venular equivalent (CRVE) were measured using the IVAN software version 1.3. Receiver operating characteristic (ROC) curves were obtained for the average retinal nerve fiber layer (RNFL) thickness and RVD indices including CRAE, CRVE, and CRAE/CRVE ratio. Areas under the ROC curves (AUCs), 95% confidence intervals (CIs), and sensitivities at a fixed specificity (>90% and >80%) were calculated. Factors related to CRAE were analyzed by simple and multiple linear regression analyses.

**RESULTS.** Among the RVD indices, the CRAE had the largest AUC for discriminating glaucomatous changes between eyes with glaucoma and those without (0.803; 95% CI, 0.742–0.855). The AUC of CRAE did not significantly differ from that of average RNFL thickness (P = 0.134). However, CRAE showed lower sensitivity than average RNFL thickness at a specificity greater than 90%. Factors significantly associated with CRAE in both simple and multiple linear regression analyses were age, spherical equivalent, average RNFL thickness, presence of diabetes mellitus, and a glaucoma diagnosis (all P ≤ 0.05).

**CONCLUSIONS.** The diagnostic ability of CRAE for detecting OAG was good, which was not much worse than that of average RNFL thickness. This finding suggests the potential usefulness of RVD for glaucoma detection.

Keywords: retinal vessel diameter, diagnostic ability, central retinal arteriolar equivalent, central retinal venular equivalent, open-angle glaucoma
tension glaucoma (LTG), and the factors related to RVD in patients with glaucoma.

METHODS

This investigation was a retrospective analysis of 145 patients with OAG and 60 healthy controls who were enrolled from a clinical database at the Glaucoma Clinic of Korea University Anam Hospital, Seoul, Korea, from January 2013 through March 2014. Ethical approval was obtained from the institutional review board. The study was conducted in adherence to the tenets of the Declaration of Helsinki.

All patients underwent comprehensive ophthalmologic examinations, including a detailed review of medical and ocular history, measurement of best-corrected visual acuity (BCVA), slit-lamp biomicroscopy, autorefraction, Goldmann applanation tonometry, central corneal thickness (CCT) measurement using a specular microscope (SP-2000P; Topcon Corporation, Tokyo, Japan), gonioscopy, and standard automated perimetry using the 30-2 Swedish Interactive Threshold Algorithm standard program (Zeiss-Humphrey, San Leandro, CA, USA). Measurements of peripapillary RNFL thickness with spectral-domain optical coherence tomography (SD-OCT; 3D OCT-1000 Mark II, software version 3.20; Topcon Corp.), dilated 30° stereoscopic photography, and 50° red-free photography (model FF 450 Plus; Carl Zeiss Meditec AG, Jena, Germany) were also conducted.

Participants included in this study met the following criteria: BCVA of greater than 20/40; a spherical equivalent (SE) between −6.0 and +4.0 diopters (D); a cylinder correction within ± 3.0 D; the presence of a normal anterior chamber and an open angle; and at least two reliable VF test results with a false-positive error less than 15%, a false-negative error less than 15%, and a fixation loss less than 20%. Subjects were excluded if they had any of the following criteria: (1) a history of ocular trauma or ocular surgery, (2) a history of any retinal disease such as diabetic retinopathy, retinal vessel occlusion, or epiretinal membrane, (3) media opacity that could affect the quality of photography, (4) optic nerve disease other than glaucoma, or (5) a history of a cerebrovascular event or systemic medication use that could affect the VF. In cases with both eyes eligible for the study, one eye was randomly chosen for inclusion.

A glaucomatous VF change was defined as the consistent presence of a cluster of three or more nonedge points on a pattern deviation plot, with a less than 5% probability of occurrence in the healthy population; a pattern standard deviation (PSD) with a less than 5%; or a glaucoma hemifield test result outside of normal limits. According to the mean deviation (MD) of the VF, the stage of glaucoma was categorized into three subgroups including early (MD ≥ −6 dB), moderate (−12 ≤ MD < −6 dB), and severe glaucoma (MD < −12 dB), as confirmed by at least two reliable VF examinations.

Open-angle glaucoma was diagnosed by a glaucoma specialist (CY) when a glaucomatous VF loss was present combined with a corresponding glaucomatous optic-disc change (neuroretinal rim thinning, notching, and excavation) or a nerve fiber layer defect. Gonioscopy was used to exclude angle closure, ruberosis, and secondary glaucoma. According to the baseline untreated IOP, the patients with OAG were categorized into two subgroups, HTG and LTG. High-tension glaucoma was defined as OAG with a baseline IOP of greater than or equal to 20 mm Hg, whereas LTG had an IOP of less than 20 mm Hg, on the basis of the Namil-Myon area of central South Korea. Data of healthy control eyes were obtained from the subjects who were referred to our clinic for a routine checkup. Inclusion criteria for healthy controls were an IOP less than 20 mm Hg without a history of increased IOP, an absence of a glaucomatous disc appearance, no visible RNFL defect on red-free photography, and a normal VF result.

Retinal Vessel Diameter Measurement

Retinal vessel diameter indices were obtained using the IVAN software version 1.3 (Department of Ophthalmology and Visual Science, University of Wisconsin, Madison, WI, USA) with the disc photographs taken on the first visit. This software is a semiautomated system used to measure the retinal vessel width from a digitized retinal image. Measurement of the RVD is described in detail elsewhere. Briefly, the sixth largest arterioles and venules passing completely through a circumferential zone 0.5 to 1 disc diameter from the optic disc margin were identified. The IVAN program automatically identified the optic disc and measured the diameters of these individual vessels, then automatically converted the arteriole and venule diameters to two variables including the central retinal arteriolar equivalent (CRAE) and the central retinal venular equivalent (CRVE), using the revised Parr-Hubbard formula. Two physicians (EY and BL) measured the RVDs of all participants to evaluate the intraclass correlation.

Statistical Analyses

The k value was used to estimate interobserver agreement of measured RVD indices (CRAE and CRVE). Receiver operating characteristic (ROC) curves were used to describe the ability of each RVD index to discriminate glaucomatous eyes from control eyes. Areas under the ROC curves (AUCs) with 95% binomial exact confidence intervals (CIs) were calculated to assess the glaucoma diagnostic ability of RVD indices (CRAE, CRVE, and CRAE/CRVE [A/V] ratio) and average RNFL thickness. Actual values from the RVD indices and RNFL were used to create ROC curves, and covariates were not adjusted. The pairwise comparisons of the AUCs were conducted for statistical significance using MedCalc (MedCalc Software Inc., Mariakerke, Belgium). Estimated sensitivities at a fixed specificity of greater than 90% and greater than 80% were reported for each parameter with the corresponding cut-off values. To identify factors related to CRAE, simple and multiple linear regression analyses were performed. The Statistical Package for the Social Sciences version 22.0 (SPSS, Chicago, IL, USA) was used for statistical analyses. All reported P values are two-sided, and differences at a level of P less than 0.05 were considered statistically significant.

RESULTS

Subject Baseline Characteristics

A total of 60 healthy eyes and 145 glaucomatous eyes (early, 134 [92.4%]; moderate, 8 [5.5%]; and severe glaucoma, 3 [2.1%] eyes) were enrolled in this cross-sectional study. The demographics of healthy subjects and glaucoma patients are summarized in Table 1. There were no statistically significant differences in age, sex, CCT, SE, and prevalence of systemic hypertension or diabetes mellitus between the control and glaucoma groups (all P > 0.05), and between the HTG and LTG groups (all P > 0.05). Baseline IOP, MD, PSD, visual field index (VFI), and average RNFL thickness differed significantly between the control and glaucoma groups (all P < 0.001). Glaucmatous eyes had an average VF MD of −3.13 ± 2.92 dB, which was classified as early-stage glaucoma. The HTG and
Systemic factors

A/V ratio 0.80

Demographic factors

CRVE, 0.974; P

CRAE, 0.100. The AUC of the A/V ratio was not significantly different from that of the CRAE (P = 0.100), not significantly different from that of the CRAE (P = 0.715). In subgroup analyses, the AUC of the CRAE in the LTG group was larger than that in the HTG group, although it did not reach a statistical significance (0.842; 95% CI, 0.771–0.897 vs. 0.753; 95% CI, 0.667–0.826; P = 0.102). The AUC of the CRAE did not differ from that of average RNFL thickness in both the HTG and LTG groups (P = 0.083 and 0.351, respectively).

Comparisons of Retinal Vessel Diameter Indices

The CRAE and A/V ratio differed significantly between the control and glaucoma groups (P < 0.001 for each). The glaucoma group had a smaller CRAE than the control group (146.21 ± 15.24 μm vs. 164.11 ± 14.76 μm, P < 0.001). Comparisons between the HTG and LTG groups showed no significant differences in the CRAE, CRVE, and A/V ratio (P = 0.085, 0.103, and 0.137, respectively; Table 2). The κ value for interobserver agreement was excellent (0.966; 95% CI, 0.955–0.974; P < 0.001).

Diagnostic Ability of Retinal Vessel Diameter Indices and Peripapillary Retinal Nerve Fiber Layer Thickness

The diagnostic values of RVD indices and peripapillary average RNFL thicknesses were compared using the ROC curve analysis (Table 3, Fig.). Among the RVD indices, the CRAE showed lower sensitivity than average RNFL thickness at a specificity of greater than 80%, the sensitivity of CRAE tended to increase more than the sensitivity of average RNFL thickness. The gap between the AUC of RNFL thickness and the AUC of CRAE had a tendency to decrease and CIs partially overlapped at a specificity of greater than 80% (Table 4).

Relationship Between Demographic and Clinical Variables and Central Retinal Arteriolar Equivalent

The relationship between demographic and clinical variables and CRAE was evaluated using simple and multiple linear regression analyses (Table 5). In simple analyses, the SE, average RNFL thickness and the presence of diabetes mellitus were positively correlated with CRAE (P = 0.001, P < 0.001, and P = 0.026, respectively) while a glaucoma diagnosis was negatively correlated with CRAE (P < 0.001). Age, sex, CCT, and the presence of hypertension did not have any association with CRAE in simple analyses (all P > 0.05). In a multiple analysis, CRAE was significantly associated with age, SE, average RNFL thickness, a glaucoma diagnosis and the presence of diabetes mellitus (P = 0.005, P = 0.004, P < 0.001, P = 0.002, and P = 0.014, respectively).

As there was a positive relationship between the presence of diabetes mellitus and CRAE in a multiple linear regression analysis, a subanalysis was conducted in nondiabetic subjects to exclude confounding effects of diabetes mellitus. A total of

LTG groups did not differ in MD, PSD, VFI, and average RNFL thickness (all P > 0.05).

Table 1. Demographics and Ocular Characteristics of Subjects

<table>
<thead>
<tr>
<th>Normal, n = 60</th>
<th>Glaucoma, n = 145</th>
<th>P Value</th>
<th>HTG, n = 63</th>
<th>LTG, n = 82</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>48.65 ± 13.88</td>
<td>51.70 ± 12.61</td>
<td>0.127*</td>
<td>51.38 ± 13.21</td>
<td>51.95 ± 12.21</td>
</tr>
<tr>
<td>Female sex, no. (%)</td>
<td>17 (28.3%)</td>
<td>62 (42.8%)</td>
<td>0.053†</td>
<td>28 (44.4%)</td>
<td>34 (41.5%)</td>
</tr>
<tr>
<td><strong>Ocular factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IOP, mm Hg</td>
<td>13.86 ± 2.37</td>
<td>18.74 ± 4.42</td>
<td>&lt;0.001*</td>
<td>22.70 ± 3.29</td>
<td>15.70 ± 2.22</td>
</tr>
<tr>
<td>CCT, μm</td>
<td>53.60 ± 32.98</td>
<td>53.02 ± 34.84</td>
<td>0.549*</td>
<td>53.86 ± 32.64</td>
<td>528.93 ± 36.65</td>
</tr>
<tr>
<td>SE, D</td>
<td>−0.68 ± 1.48</td>
<td>−1.13 ± 2.21</td>
<td>0.108*</td>
<td>−1.22 ± 2.13</td>
<td>−1.07 ± 2.28</td>
</tr>
<tr>
<td>MD, dB</td>
<td>−0.96 ± 1.41</td>
<td>−3.13 ± 2.92</td>
<td>&lt;0.001*</td>
<td>−3.09 ± 2.96</td>
<td>−3.16 ± 2.91</td>
</tr>
<tr>
<td>PSD, dB</td>
<td>2.02 ± 1.04</td>
<td>4.37 ± 3.11</td>
<td>&lt;0.001*</td>
<td>4.37 ± 3.20</td>
<td>4.38 ± 3.07</td>
</tr>
<tr>
<td>VFI, %</td>
<td>99.09 ± 0.92</td>
<td>93.61 ± 8.82</td>
<td>&lt;0.001*</td>
<td>94.88 ± 7.27</td>
<td>92.68 ± 9.75</td>
</tr>
<tr>
<td>Average RNFL thickness, μm</td>
<td>112.55 ± 8.27</td>
<td>95.21 ± 14.53</td>
<td>&lt;0.001*</td>
<td>96.41 ± 14.97</td>
<td>94.28 ± 14.19</td>
</tr>
<tr>
<td><strong>Systemic factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic hypertension, no. (%)</td>
<td>16 (26.7%)</td>
<td>53 (36.6%)</td>
<td>0.175‡</td>
<td>21 (33.3%)</td>
<td>32 (39.0%)</td>
</tr>
<tr>
<td>Diabetes mellitus, no. (%)</td>
<td>4 (6.7%)</td>
<td>15 (10.3%)</td>
<td>0.409‡</td>
<td>6 (9.5%)</td>
<td>9 (11.0%)</td>
</tr>
</tbody>
</table>

* Comparison of the two groups by Student's t-test.
† Comparison of the two groups by χ² test.

Table 2. Comparison of Central Retinal Arteriolar Equivalent and Central Retinal Venular Equivalent

<table>
<thead>
<tr>
<th>Normal, n = 60</th>
<th>Glaucoma, n = 145</th>
<th>P Value*</th>
<th>HTG, n = 63</th>
<th>LTG, n = 82</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRAE, μm</td>
<td>164.11 ± 14.76</td>
<td>146.21 ± 15.24</td>
<td>&lt;0.001</td>
<td>148.71 ± 15.99</td>
<td>144.29 ± 14.44</td>
</tr>
<tr>
<td>CRVE, μm</td>
<td>206.43 ± 18.70</td>
<td>203.11 ± 16.25</td>
<td>0.206</td>
<td>205.62 ± 16.74</td>
<td>201.19 ± 15.69</td>
</tr>
<tr>
<td>A/V ratio</td>
<td>0.80 ± 0.08</td>
<td>0.70 ± 0.08</td>
<td>&lt;0.001</td>
<td>0.71 ± 0.08</td>
<td>0.69 ± 0.08</td>
</tr>
</tbody>
</table>

* Comparison of the two groups by Student's t-test.
**TABLE 3.** Area Under the Receiver Operating Characteristics Curve of Retinal Vessel Diameter Indices and Retinal Nerve Fiber Layer Thickness

<table>
<thead>
<tr>
<th></th>
<th>Healthy vs. Glaucoma (95% CI)</th>
<th>Healthy vs. HTG (95% CI)</th>
<th>Healthy vs. LTG (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRAE</td>
<td>0.803 (0.742–0.855)</td>
<td>0.753 (0.667–0.826)</td>
<td>0.842 (0.771–0.897)</td>
</tr>
<tr>
<td>CRVE</td>
<td>0.556 (0.485–0.625)</td>
<td>0.515 (0.423–0.606)</td>
<td>0.588 (0.502–0.669)</td>
</tr>
<tr>
<td>A/V ratio</td>
<td>0.790 (0.728–0.844)</td>
<td>0.755 (0.669–0.828)</td>
<td>0.817 (0.744–0.877)</td>
</tr>
<tr>
<td>Average RNFL thickness</td>
<td>0.858 (0.805–0.905)</td>
<td>0.854 (0.756–0.895)</td>
<td>0.877 (0.811–0.926)</td>
</tr>
</tbody>
</table>

**Comparison of AUC**

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Healthy vs. Glaucoma</th>
<th>Healthy vs. HTG</th>
<th>Healthy vs. LTG</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRAE vs. RNFL</td>
<td>P = 0.154</td>
<td>P = 0.083</td>
<td>P = 0.351</td>
</tr>
<tr>
<td>CRAE vs. A/V ratio</td>
<td>P = 0.715</td>
<td>P = 0.965</td>
<td>P = 0.543</td>
</tr>
<tr>
<td>CRAE vs. CRVE</td>
<td>P &lt; 0.001</td>
<td>P &lt; 0.001</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>CRVE vs. A/V ratio</td>
<td>P &lt; 0.001</td>
<td>P = 0.005</td>
<td>P = 0.002</td>
</tr>
<tr>
<td>CRVE vs. RNFL</td>
<td>P &lt; 0.001</td>
<td>P &lt; 0.001</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>A/V ratio vs. RNFL</td>
<td>P = 0.100</td>
<td>P = 0.135</td>
<td>P = 0.177</td>
</tr>
</tbody>
</table>

**FIGURE.** The receiver operating characteristics curves for CRAE, CRVE, CRAE/CRVE (A/V) ratio, and average RNFL thickness for discriminating between normal and glaucomatous eyes in all patients with glaucoma (A), patients with HTG (B), and patients with LTG (C).
Presence of hypertension (vs. absence) / C0
Specificity > 80%
although the LTG group tended to have smaller RVD indices
diagnostic ability of CRAE between the HTG and LTG groups,
also did not observe a statistically significant difference in the
respectively).

Diagnosis of glaucoma (vs. healthy) / C0
glaucoma than in healthy eyes. The Blue Mountains Eye Study
decreased with increasing glaucoma stage independently of the
eence was found in mean arteriolar diameter between eyes with
diameter was associated with OAG incidence after adjusting for
did not show similar results, finding that a smaller retinal arteriolar
diameter was associated with OAG incidence after adjusting for

Average RNFL thickness,
l
SE, D
CCT, μm
Average RNFL thickness, μm
Diagnosis of glaucoma (vs. healthy)
Presence of hypertension (vs. absence)
Presence of diabetes mellitus (vs. absence)

19 subjects had a history of diabetes mellitus (Table 1). Therefore, 186 subjects were included in the subanalysis, which showed that the AUC of CRAE (0.800; 95% CI, 0.735–0.855) and the AUC of A/V ratio (0.793; 95% CI, 0.727–0.848) were not statistically different from the AUC of average RNFL thickness (0.864; 95% CI, 0.806–0.910, P = 0.087 and 0.088, respectively).

DISCUSSION
In the present study on the glaucoma diagnostic ability of RVD, we demonstrated that the AUC of CRAE was good and not much worse than that of peripapillary average RNFL thickness. To the best of our knowledge, this is the first report to provide diagnostic performances of RVD in patients with glaucoma.

Our observations are consistent with the findings of earlier studies that demonstrated the changes of RVD in glaucoma patients. Jonas et al. reported that the vessel diameter decreased with increasing glaucoma stage independently of the patient age. In the Singapore Malay Eye Study, both retinal arteriolar and venular diameters were narrower in eyes with glaucoma than in healthy eyes. The Blue Mountains Eye Study showed similar results, finding that a smaller retinal arteriolar diameter was associated with OAG incidence after adjusting for glaucoma risk factors. Furthermore, no significant difference was found in mean arteriolar diameter between eyes with apparent HTG and LTG in the Blue Mountains Eye Study. We also did not observe a statistically significant difference in the diagnostic ability of CRAE between the HTG and LTG groups, although the LTG group tended to have smaller RVD indices and better AUCs. In line with this, our previous study reported that mean CRAE was smaller in the young patients with LTG than in the age-matched patients with HTG. However, considering the trend of a worse VFI and a lower RNFL thickness in the LTG group than in HTG group, the better AUC of the LTG group may have been affected by the severity of glaucomatous damage rather than the diagnosis of LTG in our study.

For years, it has been controversial whether retinal arteriolar narrowing precedes or follows the development of glaucomatous damage. Previously, our group found that the RNFL thickness was significantly correlated with CRAE in LTG patients, and that central retinal artery diameter decreased over time in the progressed eyes, whereas no significant decrease in the central retinal artery diameter was seen in the stable eyes in LTG patients with asymmetric progression. Kim et al. reported that the mean diameter of the temporal retinal arterioles in the quadrants with RNFL defects was significantly smaller in patients with LTG than in those with quadrants without RNFL defects, suggesting that the decreased diameter is likely due to the decreased demand for retinal blood flow in damaged areas of the retina. On the other hand, the Blue Mountains Eye Study revealed that retinal arteriolar narrowing was associated with long-term risk of OAG and the authors proposed the concept that early vascular changes are involved in the pathogenesis of OAG. Still, our study does not give an answer to this long-standing question, but it implies that differences in the RVD may help us better detect the development or progression of glaucomatous optic neuropathy.

Table 4. Sensitivity of Retinal Nerve Fiber Layer Thickness and Retinal Vessel Diameter Indices at a Specificity >90% and >80%

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sensitivity</th>
<th>95% CI</th>
<th>Cutoff</th>
<th>Sensitivity</th>
<th>95% CI</th>
<th>Cutoff</th>
<th>Sensitivity</th>
<th>95% CI</th>
<th>Cutoff</th>
</tr>
</thead>
<tbody>
<tr>
<td>RNFL thickness, μm</td>
<td>68.28</td>
<td>60.0–75.7</td>
<td>101</td>
<td>61.90</td>
<td>48.8–73.9</td>
<td>101</td>
<td>73.17</td>
<td>62.2–82.4</td>
<td>101</td>
</tr>
<tr>
<td>CRAE, μm</td>
<td>43.45</td>
<td>35.2–51.9</td>
<td>145.10</td>
<td>39.68</td>
<td>27.6–52.8</td>
<td>145.10</td>
<td>46.34</td>
<td>35.3–57.7</td>
<td>144.32</td>
</tr>
<tr>
<td>CRVE, μm</td>
<td>8.97</td>
<td>4.9–14.8</td>
<td>180.12</td>
<td>11.11</td>
<td>4.6–21.6</td>
<td>180.12</td>
<td>7.32</td>
<td>2.7–15.2</td>
<td>177.69</td>
</tr>
<tr>
<td>A/V ratio</td>
<td>48.28</td>
<td>39.9–56.7</td>
<td>0.70</td>
<td>42.86</td>
<td>30.5–56.0</td>
<td>0.70</td>
<td>52.44</td>
<td>41.1–63.6</td>
<td>0.70</td>
</tr>
<tr>
<td>RNFL thickness, μm</td>
<td>77.93</td>
<td>70.3–84.4</td>
<td>105</td>
<td>74.60</td>
<td>62.1–84.7</td>
<td>105</td>
<td>80.49</td>
<td>70.3–88.4</td>
<td>105</td>
</tr>
<tr>
<td>CRAE, μm</td>
<td>65.45</td>
<td>55.1–71.3</td>
<td>151.20</td>
<td>52.38</td>
<td>39.4–65.1</td>
<td>151.20</td>
<td>71.95</td>
<td>60.9–81.3</td>
<td>150.95</td>
</tr>
<tr>
<td>CRVE, μm</td>
<td>19.31</td>
<td>13.2–26.7</td>
<td>190.26</td>
<td>19.05</td>
<td>10.2–30.9</td>
<td>188.64</td>
<td>19.51</td>
<td>11.6–29.7</td>
<td>190.26</td>
</tr>
<tr>
<td>A/V ratio</td>
<td>57.93</td>
<td>49.5–66.1</td>
<td>0.72</td>
<td>49.21</td>
<td>36.4–62.1</td>
<td>0.72</td>
<td>64.63</td>
<td>53.3–74.9</td>
<td>0.72</td>
</tr>
</tbody>
</table>

Table 5. Simple and Multiple Linear Regression Analyses of Central Retinal Arteriolar Equivalent

<table>
<thead>
<tr>
<th>Variable</th>
<th>Regression Coefficient</th>
<th>95% CI</th>
<th>P Value</th>
<th>Regression Coefficient</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>−0.096</td>
<td>−0.277 to 0.085</td>
<td>0.298</td>
<td>−0.277</td>
<td>−0.470 to −0.084</td>
<td>0.005</td>
</tr>
<tr>
<td>Female sex (vs. male)</td>
<td>−3.170</td>
<td>−8.011 to 1.671</td>
<td>0.198</td>
<td>1.664</td>
<td>0.542 to 2.787</td>
<td>0.004</td>
</tr>
<tr>
<td>SE, D</td>
<td>2.009</td>
<td>0.881 to 3.137</td>
<td>0.001</td>
<td>0.505</td>
<td>0.342 to 0.668</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CCT, μm</td>
<td>0.071</td>
<td>−0.007 to 0.149</td>
<td>0.072</td>
<td>13.922</td>
<td>8.011 to 1.671</td>
<td>0.198</td>
</tr>
<tr>
<td>Average RNFL thickness, μm</td>
<td>0.650</td>
<td>0.522 to 0.777</td>
<td>&lt;0.001</td>
<td>13.922</td>
<td>8.011 to 1.671</td>
<td>0.198</td>
</tr>
<tr>
<td>Diagnosis of glaucoma (vs. healthy)</td>
<td>−17.902</td>
<td>−22.473 to −13.352</td>
<td>&lt;0.001</td>
<td>−13.922</td>
<td>−22.444 to −5.400</td>
<td>0.002</td>
</tr>
<tr>
<td>Presence of hypertension (vs. absence)</td>
<td>−3.538</td>
<td>−8.520 to 1.444</td>
<td>0.163</td>
<td>9.593</td>
<td>1.995 to 17.191</td>
<td>0.014</td>
</tr>
<tr>
<td>Presence of diabetes mellitus (vs. absence)</td>
<td>9.155</td>
<td>1.096 to 17.213</td>
<td>0.026</td>
<td>9.593</td>
<td>1.995 to 17.191</td>
<td>0.014</td>
</tr>
</tbody>
</table>
Diagnosis of glaucoma typically relies on examination of structural damage to the ONH combined with measurements of visual function. Several examination tools for structural and functional assessment are used for detection and monitoring of glaucoma. Structural assessment techniques include stereoscopic or photographic examination of the ONH and RNFL and measurements of ONH configuration or RNFL thickness with imaging techniques such as confocal scanning laser ophthalmoscopy, scanning laser polarimetry, and OCT. On the other hand, functional damage of the optic nerve is assessed by standard automated perimetry. The relative importance of such examinations varies depending on the severity of glaucomatous damage. Methods to detect structural changes are more sensitive to initial glaucoma damage than are the present field testing methods. In the Ocular Hypertension Treatment Study, for example, optic disc changes were detected earlier than VF abnormalities in over half of the patients progressing to an initial diagnosis of glaucoma. In addition, measurement of peripapillary RNFL thickness with OCT has been shown to have an excellent AUC in discriminating glaucomatous eyes from healthy eyes, especially in the superior and inferior quadrants. The present study showed that RVD measurement, with AUCs of 0.742 to 0.855, could potentially be used as a supplementary diagnostic aid.

Currently, fundus photography is widely used for the purpose of routine eye examination at health screening centers and primary eye clinics because of its convenience and economic efficiency. Clinicians usually select glaucoma suspects from the database by focusing on the disc configuration, and then recommend further examinations for glaucoma diagnosis. However, owing to the inherent subjectivity of a qualitative assessment, there is considerable variability in classifying the ONH as healthy or glaucomatous both within and between graders. A patient with a large-sized normal optic disc, for instance, can have a high cup-to-disc ratio. Considering the difficulty of distinguishing real glaucomatous optic nerve change from physiologic variation, it would be helpful to obtain another clue to reinforce the suspicion of glaucoma from fundus photography. Our study showed that the AUC of CRAE was not much worse than the AUC of average RNFL thickness. The present findings suggest the potential usefulness of RVD as a second biomarker for early glaucoma detection. However, caution should be exercised when interpreting the estimates provided by RVD measurements because of the relatively low sensitivity of CRAE in this study. CRAE should not be used solely for the purpose of glaucoma screening because of its high false-negative rate. Combining the two parameters, ONH morphology and RVD, may yield better glaucoma diagnosis.

In this study, multiple linear regression analysis showed that older age, a more myopic eye, lower average RNFL thickness, and a glaucoma diagnosis were related to narrower retinal arterioles. These results are in agreement with those of previous studies. Several studies demonstrated the inverse relationship between age and RVD. Paton et al. reported that increased axial length was associated with narrowing of both arteriolar and venular diameters. They suggested that narrower RVD in association with increased axial length may represent not only a magnification effect but also an actual biologic process. In the present study, we did not include axial length in the multiple regression analysis because of a high multicollinearity between SE and axial length. However, a longer axial length was associated with a smaller CRAE in a simple regression analysis ($P = 0.018$). It has been widely accepted that refractive error is generally the result of anomalies in axial length. This study has some limitations. First, the current study was not population based, but hospital based. Moreover, most of the glaucoma patients included in this study had early glaucoma. Therefore, our data might have been subjected to selection bias. Second, RVD might have been confounded by systemic diseases and medications. The Atherosclerosis Risk in Communities and the Beaver Dam Eye Study reported negative correlations between blood pressure and retinal arteriolar diameter. Atherosclerosis and diabetes mellitus are known to be associated with RVD. In the current study, hypertension was not associated with CRAE, but the presence of diabetes mellitus was positively correlated with CRAE. The relationship between atherosclerosis and CRAE could not be assessed due to limited information of systemic disease. In addition, the combined use of aspirin and antihypertensive agents was found to be related to wider retinal arteriolar diameter by the Blue Mountains Eye Study. Howard et al. also found an effect of systemic medications on RVD. Because most of the subjects with systemic hypertension had been on medications in this study, it could have affected our results. Given the high prevalence of such systemic diseases in elderly persons, the clinicians should consider the patient’s medical history when using RVD for glaucoma diagnosis. Third, although the interobserver agreement was excellent in this study, manual adjustment is necessary when measuring the RVD, because measurements of CRAE and CRVE by IVAN software are not fully automated.

In summary, CRAE had a good diagnostic ability to detect glaucoma in healthy subjects, and its diagnostic capability was not much worse than that of peripapillary RNFL thickness measured by OCT. These findings suggest the potential usefulness of RVD as a supplementary biomarker to the conventional methods used for glaucoma diagnosis.

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References


