Using the Arteriolar Pressure Attenuation Index to Predict Ocular Hypertension Progression to Open-angle Glaucoma

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Background: Vascular phenomena are considered important to optic nerve and visual field progression in open-angle glaucoma (OAG). A recently described formulation, the Pressure Attenuation Index (PAI), links arteriolar caliber variations to pressure loss along the retinal arteriolar system.

Objective: To examine whether the PAI could predict ocular hypertension (OHT) progression to OAG.

Methods: The PAI was calculated for 27 eyes of 14 patients with OHT using initial and final digitized optic disc photographs taken during a follow-up interval of 5 to 18 years. Serial stereo color disc photographs and visual fields were analyzed to determine progression.

Results: At baseline, the arteriolar tree of 8 subjects with OHT that progressed to OAG (n=8 eyes) demonstrated a 45.8% greater mean PAI value than that of 7 subjects who did not progress (n=7 eyes) (mean±SEM, 5.31±0.93 vs 3.64±0.34; r=0.83). Progression was independent of baseline cup-disc ratio. The PAI values of subjects with stable OHT remained stable after a median follow-up interval of 12.0 years. The PAI values of subjects with OHT that progressed demonstrated a further increase of 19.97%±11.24% during a median follow-up period of 6.0 years.

Conclusions: The results support the hypothesis that low end-arteriolar pressure predicts the progression from OHT to OAG. The PAI provides a new, early, reproducible, and physiological method to study vascular phenomena in glaucoma.

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V ASCULAR PHENOMENA are considered important to the evolution of optic nerve and visual field progression in open-angle glaucoma (OAG).[1-11] Patients with ocular hypertension (OHT), low-tension, and high-tension glaucoma demonstrate retinal arteriolar narrowing compared with healthy controls.[2,3] Numerous histopathological studies reveal optic disc capillary changes in glaucoma, including dropout proportional to the extent of optic atrophy, but capillary functional capabilities remain unknown.[4-7] Rheological influences or intrinsic endothelial changes may contribute to such changes.[7-11] The link between changes in ocular perfusion pressure and OAG progression also points to the importance of vascular phenomena in OAG.[12]

Recently, from a model based on physiological laws governing blood flow in living vessels, a new index was derived and tested to relate retinal vessel caliber changes to pressure-attenuating effects.[13] The Ohm law, which relates pressure differential along a tube to flow and resistance, the Poiseu-

ille formulation of resistance to flow along a tube, and the Murray law, which describes flow in blood vessels, were combined to create a new formulation. This states that the pressure differential along a vessel is proportional to its length (L) and inversely proportional to its diameter (D). The proposed term Pressure Attenuation Index (PAI) is expressed algebraically as PAI=L/D. The telecentric fundus camera permits analysis of the PAI directly from optic disc photographs.[13-17] Because healthy individuals share a common PAI value, significant alterations in PAI values have been shown to reflect either axial ametropia or a pathophysiological change in the retinal arterioles themselves.[13]

The PAI links measured retinal diameter changes to retinal arteriolar pressure dissipation and reduced end-arteriolar pressure. Arteriolar microvascular changes demonstrated in OAG[2-7] might therefore be a measure of reduced end-arteriolar pressure compared with that of healthy subjects. This prompts the question of whether patients with OHT that progresses to OAG demonstrate an altered PAI compared with
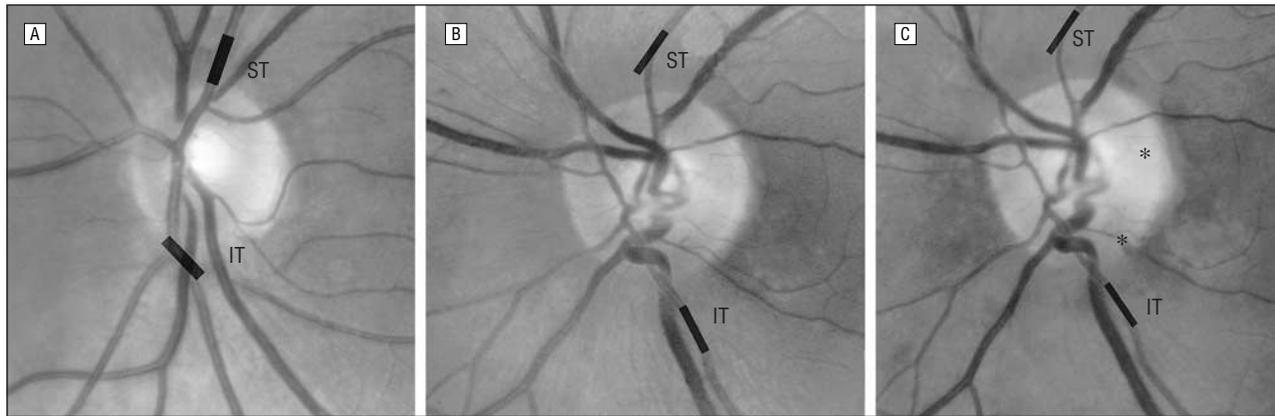
Figure 1. Sample images of stable and progressed optic discs depict arteriolar Pressure Attenuation Index (PAI) test locations and examples of progression. A, Sample initial photograph of a stable optic disc of a subject with ocular hypertension; 120-pixel–length cylinders of known diameter are superimposed on a nonconstricted segment of the dominant arteriole of the superotemporal (ST) and inferotemporal (IT) quadrants as it arises out of the disc margin. B, Sample initial photograph of the disc of a subject with ocular hypertension and a high PAI value (narrowed arterioles). The mean PAI value is 5.27. C, Final photograph of the same subject depicted in B (14-year interval). The mean PAI value has increased to 6.06 (approximate rate of progression, 1% per year). The position of the arterioles (asterisks) has shifted, and there is thinning of the rim on stereo disc photographs at both locations when comparing B and C. The cup-disc ratio in B is equal to or smaller than that in A, yet the PAI values are different.

patients with stable OHT. The PAI prediction of OHT progression to OAG could provide a new and early means of quantifying and following this risk and would provide a unique understanding of the pathophysiological processes of OAG.

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METHODS

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PATIENT SELECTION CRITERIA

We reviewed the medical records of all patients aged 35 years or older who were seen at the Duke University Eye Center, Durham, NC, from 1970 through 1995 with a diagnosis of OHT or who were considered to be glaucoma suspects.

Selection criteria were as follows: (1) Subjects were required to have the diagnosis "ocular hypertension" (corneal thickness–corrected intraocular hypertension of more than 21 mm Hg)[18,19] or to be considered "glaucoma suspects" purely on the basis of corrected elevated intraocular pressure (IOP) above 21 mm Hg and not because of increased disc cupping or asymmetry; (2) Subjects were required to have had color stereo optic disc photographs taken in 1995 or earlier and at least 1 more set of follow-up photographs taken during a minimum interval of 5 years (actual range, 5-18 years; median, 10.5 years); and (3) Two or more reliable visual fields[20] and a normal initial visual field were required during a period of at least 3 years (actual range, 3-8 years; median, 6 years).

Exclusion criteria were as follows, to eliminate a potential underlying influence on baseline arteriolar diameters: (1) cup-disc ratios of greater than 0.7; (2) a history of diabetes mellitus or insipidus; (3) diagnosis of retinitis pigmentosa; (4) history of smoking; (5) use of systemic vasoactive medications; or (6) refractive errors of 4 diopters or more of spherical equivalent, because this correlates with a predominant axial component.[21]

OUTCOME MEASURES

All serial stereo color optic disc photographs were compared for progression and classified by secret ballot by 2 observers masked to subject identification and diagnosis. Criteria for disc progression included generalized or focal enlargement of the cup, notching of the rim, nerve fiber layer loss, increased ex-

posure of the lamina cribrosa, superficial splinter (Drance) hemorrhage, focal pallor changes, and baring of blood vessels and/or a shift in their angle of emergence off the disc or off a parent vessel. If these observers disagreed, 3 different masked observers analyzed the photographs and classified them by secret ballot. Visual field progression was determined by using criteria employed by the Collaborative Normal-Tension Glaucoma Study Group.[20]

To study potential confounding variables, all charts of patients satisfying inclusion and exclusion criteria were reviewed for the following information: age at diagnosis, age at the time of the initial photograph, sex, family history of glaucoma, race, systemic hypertension, right vs left eye, and follow-up interval. Analysis of IOP data included IOP at the time of the initial photograph, the presence of an IOP greater than 21 mm Hg, the mean or corrected mean (for central corneal thickness) IOP,[18,19] corrected mean IOP greater than 21 mm Hg, and IOP of 30 mm Hg or more. Data on treatment at the time of the initial photograph, the number of topical and oral agents used, the occurrence of laser or surgical therapy, and the use of specific topical and oral agents, including β-agonists, β-blockers, carbonic anhydrase inhibitors, α-agonists, miotics, or a prostaglandin agonist were also obtained.

IMAGE ANALYSIS

As previously described,[13] retinal images were captured with a telecentric fundus camera (Zeiss camera; Carl Zeiss, Inc, Oberkochen, Germany; 15° in the current study). These slide images were scanned directly into Adobe Photoshop, version 5.0 (Adobe Systems Inc, San Jose, Calif) in grayscale. A minimum resolution of 1200 dpi was selected to lessen the pixelation and to permit better vessel edge definition for diameter measurements. No image modification was performed. Given that the central retinal artery arborizes at the disc with a dominant vessel per quadrant, the diameter of the largest arteriole in the superotemporal and inferotemporal retinal quadrants was measured (in pixels) on each photograph as near to the disc as possible in a segment of uniform caliber.[13] The vessel diameter was determined by matching its diameter to the diameter of a measurable cylinder of 120-pixel length that is superimposed on the vessel. Three masked measurements were taken for each vessel (**Figure 1**).

The total length in pixels of the largest retinal arteriole in the superotemporal and inferotemporal quadrants is measured from the origin of the arteriole at the disc to a point 7.5° peripherally using computer software (Adobe Photoshop).[13] This 7.5° is an arbitrary angle that represents 600 pixels on our images. The value of L, when used in the present context of an analysis of pressure dissipation along the entire length of the retinal arteriolar tree, did not differ between subjects with OHT and OAG in this study ($P = .49$). Thus, the total length, in pixels, of the largest retinal arteriole in each quadrant was taken as a constant (arbitrarily 100 pixels) for our study population. The value of L becomes important in cases of increased vessel tortuosity or when performing segmental vessel analyses, described below.

The calculation of the PAI along each arteriolar segment is performed according to our formula $PAI = L/D = k(100/D)$. The value of k is 6.02×1.1 or 6.62 and simply serves as a constant of proportionality to compare PAI values across studies. In the current study, a smaller value of L was used instead of 602.2603 used previously,[13] which results in a proportionately smaller PAI value in the current report by a factor of 602.2603/100 or 6.02. The scanned image size of 1200 pixels, vs 1090 pixels in a previous report,[13] magnifies the measured diameter and thereby results in a proportionately smaller PAI value by a factor of 1200/1090 or 1.1. The PAI value for each retinal quadrant is then averaged to obtain the PAI value for each subject. The PAI analysis was performed on initial disc photographs and final follow-up photographs obtained on each subject.

Finally, we calculated the absolute pressure attenuation in millimeters of mercury that would occur in the retinal arteriolar system to confirm the clinical significance of the downstream effect of a given PAI value. The relevant diameter and length measurements of nonbranching arteriolar segments, from the origin of the central retinal artery to the reproducible limit of resolution of the vessels in their course towards the fovea (30 to 40 μm), were calculated in the digital fundus images in the same manner as described above. When used in segmental vessel analysis, the value of L becomes a specific function of the vessel studied, and the Poiseuille law is used to convert the PAI value, as L/D, directly into a perfusion pressure calculation in millimeters of mercury.[13]

STATISTICAL ANALYSIS

For statistical analysis of OHT progression, only one eye of each subject was chosen, at random, in case of any dependency between eyes of the same individual. In one patient, one eye progressed and the other did not, so both eyes were included in the analysis because this dependency was not demonstrated. Thus, of the 14 patients enrolled in this study, for 13 subjects, one eye of each was included in the analysis, and, for one subject, both eyes were included, for a total of 15 eyes. A point-biserial comparison was performed based on the mean PAI values of the subjects studied. Interobserver variance, intraobserver variance, and percentage difference calculations in mean PAI values from the initial to the final photograph involved the use of all subject eyes in the study. Where appropriate, a 2-tailed t test was applied.

RESULTS

Fourteen eyes of 7 subjects progressed by optic nerve criteria, and 1 eye progressed by visual field criteria. All subjects had normal visual fields at baseline. Only 1 eye later developed a new visual field defect, and this subject demonstrated corresponding optic nerve head progression as
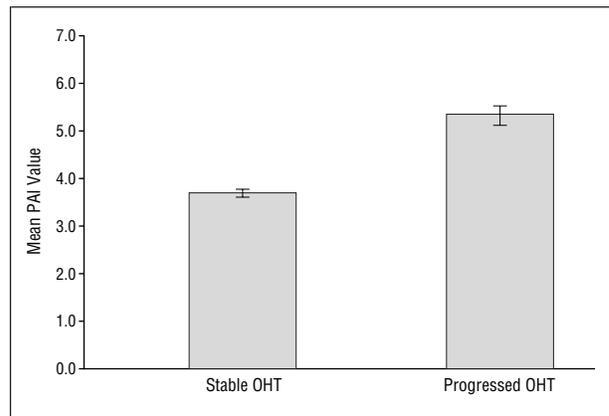

Figure 2. Mean arteriolar Pressure Attenuation Index (PAI) variation in subjects with stable or progressed ocular hypertension (OHT). The mean PAI value was 45.8% greater in subjects with progressed OHT.

well. The vertical cup-disc ratio ranged from 0.13 to 0.70 (median, 0.45). No correlation was found between OHT progression to OAG and vertical cup-disc ratio, cup-disc ratio of 0.4 or more, the presence of focal disc changes, initial visual field results, and the presence of visual field progression.

Demographic variables, including subject age at diagnosis, age at the time of the initial photograph, sex, family history of glaucoma, race, systemic hypertension, and right vs left eye, did not correlate with OHT progression. The follow-up interval was longer for the stable OHT group vs the progressed OHT group (median, 12.0 years vs 6.0 years, respectively) but did not correlate with OHT progression. The difference in PAI values between the groups was also not explained by the IOP value at the time of the initial or final photograph, the presence of an IOP greater than 21 mm Hg, the mean or corrected mean (for central corneal thickness) IOP,[20] corrected mean IOP greater than 21 mm Hg, and IOP of 30 mm Hg or more.

The act of treatment at the time of the initial photograph, the number of topical and oral agents used, the presence of laser or surgical therapy, and the use of specific topical and oral agents, including β-agonists, carbonic anhydrase inhibitors, α-agonists, miotics, or a prostaglandin agonist, did not correlate with OHT progression to OAG. The use of a β-blocker at the time of the initial photograph was also not correlated with OHT progression to OAG, but β-blocker use during the ensuing follow-up period correlated with less progression. The PAI prediction of OHT progression, based on the initial and final photographs, demonstrated the ability to predict OHT progression to OAG among subjects taking β-blockers and subjects not taking β-blockers.

A bar graph (**Figure 2**) illustrates that subjects with OHT that progressed demonstrated PAI values that were 45.8% higher than those of subjects with OHT that did not progress, as determined from initial disc photographs ($r = 0.83$; point-biserial). Raw data analysis, of subjects with progressed vs stable OHT reveals 2 nonoverlapping distributions with a PAI value range of 3.11 to 4.07 (mean ± SEM, 3.64 ± 0.34) for stable OHT vs 4.26 to 7.24 (mean ± SEM, 5.31 ± 0.93) for progressed OHT, providing an interval of 0.19 units (**Figure 3**). A correla-
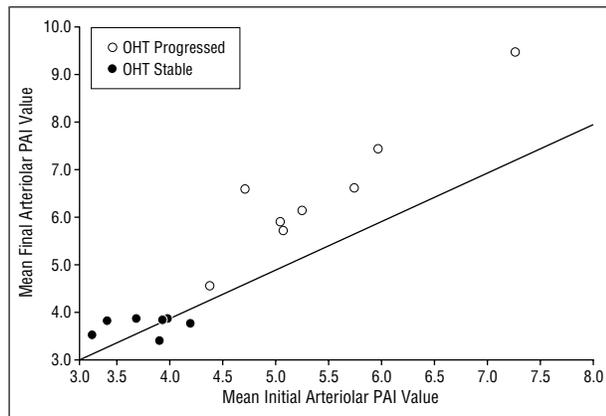
Figure 3. Scatterplot of the mean arteriolar Pressure Attenuation Index (PAI) values based on initial and final analyses of subjects with stable or progressed ocular hypertension (OHT).

tional analysis revealed no significant interrelation between eyes in the analyses performed.

During a median follow-up of 6.0 years, the mean PAI values of the group with progressed OHT (n=8 eyes of 8 patients) increased further from the baseline value by 20.0%±11.2%. This increase in PAI values was greater ($P<.001$) than that seen in subjects with stable OHT. In the latter group (n=7 eyes of 7 patients), the PAI values remained essentially unchanged (mean increase, 1.0%±3.1%) during the median follow-up period of 12.0 years. The PAI value from initial photographs was predictive of later quadrant-specific progression for both the superotemporal ($P<.001$) and inferotemporal ($P<.001$) quadrants.

The PAI provided a reproducible value for vessel diameter with a masked intraobserver variation of 0.5% and an interobserver variation of 1.1% by intraclass correlation analysis, which is slightly better but still comparable to the results of others.[13,22] Further analysis revealed no difference in ocular pressure before and after pupillary dilation for photography (data not shown). As described in other applications of the PAI,[13] all groups shared comparable arteriolar tree arborization parameters, and no difference was noted in the mean vessel length from any one quadrant to another in either of the groups (data not shown).

COMMENT

The significant associations of low ocular perfusion pressure[12] and other vascular changes in low-tension and high-tension glaucoma[1-12,23] prompted the question of whether retinal blood flow could predict the progression to OAG prior to the development of increased optic disc cupping. Therefore, we applied a measure of the pressure effects of retinal arterioles in different eyes.[13] The PAI describes the relationship between arteriolar vessel geometric measurements (length and diameter) and hydrostatic pressure attenuation in a given retinal arteriolar system. In addition, because of the Murray law, we are able to infer downstream vessel caliber and, hence, pressure attenuation through the arteriolar system from the largest arteriole measured.[24]

Several studies support the retinal arteriolar changes noted in disc photographs of patients with OAG, including a spatial correlation between blood vessel diameter reduction or fluorescein filling defects and the location of the visual field defect.[2,25-27] Although arteriolar diameters have been shown to be reduced in advanced vs early-onset glaucomatous optic nerves, our study is the first to demonstrate an index that could predict such progression based on initial photographs. The PAI predictions of future progression do not prove that vascular changes are the primary cause of progression because such changes may serve as a very early marker of a process of degeneration already in progress. Nevertheless, such a marker might represent a very early step in glaucomatous progression. Furthermore, the arteriolar narrowing, which is found more frequently in subjects with normal-tension glaucoma compared with subjects with ocular hypertension and high-tension OAG,[28] may represent an increased susceptibility to vascular influences and their influence on progression.

The 45.8% smaller arteriolar diameter of subjects with progressed OHT, determined from our initial disc photographs, is greater than the 18.5% or 16.5% to 17.7% decreases reported previously.[2,26] Our measurements compare very different subjects, specifically those with similar cup-disc ratios, central corneal thickness–defined cases of ocular hypertension, and photographs corrected for magnification differences. For instance, when magnification factors are controlled for and focal arteriolar thinning is examined with respect to a fixed neuroretinal rim area, differences of approximately 15% to 60% are noted.[25]

The question arises as to whether changes in arteriolar vessel calibers remain stable over time or represent temporal fluctuations or artifacts. In glaucomatous and healthy subjects with stable optic discs, arteriolar caliber measurements have been demonstrated to be consistent between visits after 8 to 93 months of follow-up (median, 37 months), suggesting that such changes are not related to ocular pulsations or vasospastic or other short-acting mechanisms.[25] Furthermore, measurements of arteriolar diameters are not affected by acute blood pressure variations.[25,27-28] The mean PAI value of 3.64 is only 0.4% lower than the scaled equivalent of the value obtained previously in a bank of historically healthy controls ($P=.92$).[13] The conservation of the PAI from initial to final photographs in the stable OHT group further reinforces the pathological nature of the PAI increase over time in subjects with progressed OHT.

It would be interesting to address the clinical significance of a change in PAI values in terms of actual arteriolar pressure changes. The PAI is unique in that it allows the conversion of segmental arteriolar branch length and diameter data into an actual perfusion pressure differential through the Poiseuille law.[13] A previously derived calculation of the absolute pressure attenuation in the retinal arteriolar system demonstrated that the hydrostatic pressure drop occurring along the retinal arteriolar system from the disc to a vessel of 30 µm to 40 µm in size will be of the order of 15 mm Hg in healthy subjects.[13] If we assume that all vessels shrink in the same proportion in subjects with progressed glaucoma and we

assume that the increase in plasma viscosity in subjects with low- and high-tension OAG is on the order of 3.6%,[9] then the Poiseuille law predicts that this 15 mm Hg pressure attenuation will be increased to 15.5 mm Hg.[29,30] These pressure changes are comparable to measured pressure attenuations occurring in other vascular systems for vessels of this caliber.[30] The initial PAI value indicates that in the eye with OHT that progresses to OAG, a 45.8% greater pressure dissipation will occur because of the extreme arteriolar narrowing. As such, a 7.1 mm Hg increase in pressure attenuation over healthy subjects has occurred in the retinal arteriolar tree of patients with progressed OHT down to the 30-μm to 40-μm vessel size. During a further median follow-up interval of 6.0 years, the 20.0% increase in the PAI values of subjects with progressed OHT would contribute an additional 3.1 mm Hg pressure loss, for a total pressure loss of 10.2 mm Hg more than subjects with stable OHT. Thus, the PAI is a measure of a real and potentially clinically significant pressure drop across the retinal arteriolar tree of subjects with progressed OHT.

The PAI predicts that conditions associated with increased arteriolar length or reduced diameter would result in a significant downstream pressure loss. Interestingly, axial myopia induces a reduction in end-arteriolar pressure by virtue of the long course blood must travel along the retinal arteriolar tree, compared with emmetropia.[13] In fact, axial myopia serves as a significant risk factor for progressive visual field loss.[31] Although one would expect that local control mechanisms should effect the necessary adjustments to regulate flow and pressure to the capillaries, the glaucomatous vascular system may demonstrate an abnormal autoregulatory capacity.[32] An inability of the retinal vessels to upregulate capillary bed blood flow when required might predispose patients to relative peripheral retinal ischemia. Low end-arteriolar pressure may therefore provide the common denominator for OAG progression that is shared by low ocular perfusion pressure and the ocular conditions associated with thin and/or long retinal arterioles.

The mechanism of the retinal arteriolar pressure reduction observed in OAG is not known. The vascular endothelial abnormalities described in OAG are interesting in light of the protective effects of an inhibitor of nitric oxide synthase isoform 2 on ganglion cell loss, independent of IOP control.[33] The endothelium and its products may play an important role in many areas of the eye, including retinal arterioles, optic nerve vessels, ganglion cell apoptosis, and trabecular meshwork permeability.[7,33-39] Interestingly, endothelin-1 microapplication into the retrobulbar optic nerve of rabbits and rhesus monkeys induces a 35% to 38% decrease in optic nerve blood flow with corresponding arteriolar narrowing, optic disc excavation, and histologic tissue loss from the induced ischemia.[36] Because optic nerve blood flow is less easily studied than is retinal blood flow,[40] PAI analysis of retinal circulatory changes may assist in the quantification of such influences and the complex pathophysiological process.

Other mechanisms may explain the predisposition to retinal ganglion cell death in subjects with progressed OHT, including possible nonlinear effects of plasma viscosity and shear stresses and other resistance factors as the smallest vessels are encountered. Also, changes in retinal vessels may serve as a surrogate for parallel changes in the perfusion system of the lamina cribrosa. The PAI and its progression may even serve as a marker of an otherwise undetectable retinal ganglion cell loss that may have already been underway in subjects with progressed OHT, even at the time of their baseline visit.

Although conflicting data exist as to the actual progression rate in OAG, the disease clearly does not progress in all patients.[41,42] The ideal situation would be to detect patients who will eventually progress so as to appropriately distribute aggressive therapy. A better situation would involve the detection of such high-risk subjects prior to their losing significant visual function. Our study is the first to quantify a difference between OHT that progresses compared with OHT that does not, independent of a difference in cup-disc ratio. The PAI prediction of progression occurred prior to the development of any glaucomatous visual defects and was a more sensitive indicator of progression because only 1 of 27 eyes progressed by visual field criteria. The PAI provides a more sensitive and reproducible marker of OHT progression than cup-disc measurements, visual field changes, and clinical impression of progression. Because the changes in arteriolar diameters and nerve fiber layer thicknesses may reverse after glaucoma therapy,[43,44] it is possible that the PAI may serve as a physiological treatment end point or target variable. The PAI permits a physiological analysis that we believe results in a more comprehensive understanding of the pathogenesis of OAG progression from OHT and hence a rationale for future therapies and studies.

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Call for Papers

J*AMA* and the ARCHIVES journals will be participating in the 2003 global theme issue, "Pain Management." We invite all investigators to submit their best research addressing issues concerning pain management in ophthalmology for consideration for the November 2003 issue. Manuscripts received by May 1, 2003, have the best chance for acceptance for the global theme issue. Manuscripts not accepted for the theme issue may be considered for other issues of the ARCHIVES. All manuscripts are subject to our usual peer review. Please note in the cover letter that the submission is for the November 2003 "Pain Management" issue.