Relationship between Diastolic Perfusion Pressure and Progressive Optic Neuropathy as Determined by Heidelberg Retinal Tomography Topographic Change Analysis

Patrick Quaid,[1,2] *Trefford Simpson,*[1] *and Thomas Freddo*[1]

Purpose. To determine through retrospective file analysis which clinical factors best predict glaucomatous optic neuropathy as evaluated by Heidelberg retinal tomography (HRT II) imaging.

Methods. One hundred twenty-two records from patients referred for HRT imaging at the University of Waterloo Ocular Heath Clinic met inclusion criteria for this study and were reviewed. Topographic change analysis (TCA) data generated by HRT were examined in addition to the following clinical information: diastolic blood pressure, right arm sitting, intraocular pressure, and central corneal thickness. All HRT scans included were required to have 20 μm or better standard deviation (SD) on acquisition and deemed "very good" quality or "excellent" by HRT software. Based on previously defined published HRT TCA change criteria, each patient was allocated to one of the following groups: stable, borderline, or progressive.

Results. Diastolic perfusion pressure (DPP) was found to be significantly lower in the borderline and progressive groups compared with the stable group ($P < 0.001$). DPP was also lower significantly lower in the progressive group compared with the borderline group ($P < 0.001$).

Conclusions. Low DPP appears to be a reasonable predictor of progressive optic neuropathy as determined using scans of <20 μm SD on the HRT TCA platform. DPP of 56 mm Hg or lower appears to be a clinically useful threshold to identify patients at increased risk of progressive optic neuropathy. (*Invest Ophthalmol Vis Sci.* 2013;54:789–798) DOI:10.1167/iovs.12-11177

Glaucoma, ultimately defined as a progressive optic neuropathy, is the second leading cause of irreversible blindness worldwide[1] and affects over 60 million people worldwide, with more than 10% of these patients classified as blind.[2] These numbers are conservatively expected to rise by 25% to 30% by 2020.[3] The causative factors for glaucoma remain elusive, and the link between blood pressure and intraocular pressure is of particular interest. Of all glaucoma subtypes, primary open-angle glaucoma (POAG) will comprise approximately 74% of cases by 2020, with the so-called normal tension glaucoma (NTG) subtype estimated to be present in approximately 20% of these POAG cases.[4] Although there is consensus that NTG is simply a form of open-angle glaucoma (OAG) without the typical elevated intraocular pressure (IOP), there appears to be no research that has concretely linked perfusion pressure to an objective, quantitative measure of glaucomatous optic nerve progression.

Numerous large-scale studies such as the Barbados Eye Study,[5] the Singapore Malay Eye Study,[6] and the Baltimore Eye Study[7] have found an increased risk of OAG with lower diastolic perfusion pressure (DPP). Evidence from these large-scale studies suggests that blood pressure plays at least a role in OAG, with estimates of a 2- to 6-fold increase in prevalence of OAG in patients with DPPs lower than 55 mm Hg.[8,9] NTG is more common in countries such as Japan, where the prevalence of NTG is approximately 3-fold that of POAG[10] and the diastolic blood pressure (DBP) tends to be lower compared with Western countries.[11] The suspicion of a link between lower DPP and increased glaucoma risk is not new. Indeed the Rotterdam Eye Study[12] demonstrated an increased risk of OAG for patients on calcium channel blockers specifically after 6.5 years of follow-up (relative risk 95% confidence interval being 1.1–1.3), an effect not found with beta-blockers. This finding is interesting given that calcium channel blockers reduce blood pressure but not IOP, whereas systemic beta-blockers cause both a reduction in blood pressure and IOP, thus likely affecting perfusion pressure to a lesser degree.

Although not universally accepted, some studies have also shown that hypertension (while certainly a cardiovascular concern) may actually be a protective factor in glaucoma[13–17] with the degree of this "protection" decreasing with age, possibly due to increased atherosclerosis.[17] This may explain some of the contradictory findings showing no protective effect of hypertension in older patients.[18] There is also a higher frequency of NTG in females compared to males, especially in Asian studies,[19] which is notable considering that hypertension is more prevalent in males compared to females in almost all ethnic groups.[20] Quantitative evidence of increased optic neuropathy with lower perfusion pressures has remained somewhat elusive, however.

The clinical challenge in glaucoma is to detect definitive progressive optic neuropathy as early as possible to justify therapeutic or surgical intervention in order to avoid future vision loss. It is understandable that most glaucoma studies use moderate to advanced glaucomatous cases (with or without

From the [1]University of Waterloo School of Optometry & Vision Science, Waterloo, Canada, and the [2]Private Practice, Guelph, Ontario, Canada.

The authors alone are responsible for the content and writing of the paper. The authors have full control of all primary data and agree to allow review of their data upon request.

Submitted for publication October 19, 2012; revised December 4, 2012; accepted December 12, 2012.

Disclosure: **P. Quaid**, None; **T. Simpson**, None; **T. Freddo**, None

Corresponding author: Patrick Quaid, University of Waterloo School of Optometry & Vision Science, Waterloo, Ontario, N2L 3G1, Canada; ptquaid@sciborg.uwaterloo.ca.

visual field loss) because early progressive optic neuropathy can be difficult to definitively diagnose. It is our opinion, however, that studies examining patients with risk factors who "convert" to glaucoma over time will ultimately reveal the underlying pathophysiology of glaucoma. This study is novel in that it reports the association between DBP, IOP, and central corneal thickness (CCT) in relatively early progressive optic neuropathy cases as defined by using Heidelberg retinal tomography topographic change analysis (HRT TCA) software and relatively stringent image acquisition criteria. Controlling noise levels as much as possible in any form of imaging would seem to be critical when the ultimate purpose of the imaging is to detect change. Under some circumstances, progression could be defined as "change outside of noise"; therefore, in this study we chose a previously used criterion in addition to stringent imaging quality control measures to determine the relationship between HRT TCA progression and various risk factors. The HRT manual appears to be the only guideline to date to define an acceptable standard deviation (SD), with a standard deviation of 50 μm or less being suggested, which has been quoted in prior studies.[21] More stringent criteria (images with an SD of 20 μm or less) were used in the current study.

Examining the equation for DPP (DPP = DBP − IOP)[16] also raises an inevitable question: At what DPP level should clinicians be concerned and can the DPP level be used to predict future progression? To this end, this study examined eligible records of patients with various OAG risk factors and with intact visual fields who were referred to a university-based imaging center, in order to determine the predictor variables associated with early progression as evaluated by HRT TCA. To our knowledge, this is the first study to specifically report on the association between DPP and progression rates using HRT TCA using relatively stringent acquisition criteria.

Methods

University of Waterloo School of Optometry (UWSO) HRT clinic database records of patients referred for HRT II imaging within the last 4 years were retrospectively examined. Eligible records had to have a minimum of three scans, with each scan being required to have an SD of 20 μm or less with "very good" quality indicated on the HRT printout for all sessions. A minimum 9-month monitoring period was required from the first scan to the most recent scan. All patients selected were required to have seen the first author in the UWSO ocular health clinic at their most recent clinical evaluation and have had IOP, CCT, and DBP (right arm sitting) measured in addition to HRT imaging. All patients taking systemic blood pressure medications were excluded. Patients with any repeatable documented visual field loss were excluded. Using these relatively stringent selection criteria, 122 patient records were eligible for analysis.

To our knowledge, HRT is currently the only imaging device to report and quantify in micrometers the SD of the scan attained. Ultimately, progression is determined as "change outside of noise" for any clinical parameter, thus it is logical to assume that in order to determine change one needs to accurately know the "noise" of the clinical measure in question. This premise was used in determining whether any particular subject was showing progressive optic neuropathy over time, which of course is the hallmark of glaucoma. While there may have been other measures that could have been used, the micrometer change on TCA was ultimately chosen because it is quantifiable and relatively independent of subjective interpretation, can be interpreted in relation to the noise of the method used to acquire the data (i.e., the SD of the HRT scan), and previous publications are available to support the use of HRT TCA change criteria.[22]

Details on the exact TCA methodology have been described elsewhere,[23] with the basic methodology of HRT TCA essentially involving an analysis of variance (ANOVA) approach comparing each HRT scan to the baseline scan and showing probability symbols for locations with statistically significant change (i.e., red for progression). Each eligible UWSO record was reviewed and assigned to one of three groups based on HRT TCA results using previously published HRT TCA criteria including both mean depth change and disc area.[22] All scans in this study were required to have an SD of 20 μm or less with the HRT printout stating "very good" or "excellent" in terms of image quality. Based on the HRT TCA change, each eligible record was allocated to one of the following groups:

1. Stable (liberal criterion: probably no change). Change observed in TCA mean depth data in a 0- to 50-μm range (i.e., 0–2.5 SD) in area under 1% of disc area (DA).
2. Borderline (moderate criterion: probable change). Change observed on TCA mean depth of >50 μm but <100 μm (i.e., 2.5–5 SD) in area greater or equal to 1% of DA.
3. Progressive (conservative criterion: definite change). Change observed on TCA mean depth data of 100 μm or more (i.e., >5 SD) in an area greater or equal to 2% DA.

All eligible files had at least three HRT images, with the following measurements done at minimum by the first author as part of the routine clinical care: IOP via Goldmann applanation tonometry, DBP measured manually using an appropriately sized cuff (right arm sitting) after a 5-minute rest, and CCTs using a Reichart pachymeter. DBP was measured manually in the clinic within 10 minutes of measuring IOP and CCTs and was taken twice, with the average result being recorded. IOP, CCT, and DBP measurements all had to have been taken at the last HRT session prior to imaging. This study was approved by the Office of Research and Ethics at the University of Waterloo and adhered to the tenets of the Declaration of Helsinki.

Statistical Analysis

Data were analyzed using Statistica 7 (Statsoft, Inc., Tulsa, OK) and R 2.15 (Development Core Team, 2011; R Foundation for Statistical Computing, Vienna, Austria, http://www.R-project.org/). ANOVAs and the Student's *t*-test was used to examine differences between means and regression trees (using R package party) and receiver operating characteristic (ROC) curves (using R packages Epi and pROC) were used to determine what predictors influenced the subject groupings.

Results

From the 122 records qualifying for review, 16 patients were classified as progressive, 24 patients as borderline, and 82 patients as stable (Table). The average number of scans (minimum of three required) was similar between groups (4.86 for the progressive group, 4.17 for the borderline group, and 4.58 for the stable group) as was the mean time of follow-up (minimum of 9 months required) for each group (28.84 months for the progressive group, 30.17 months for the borderline group and 29.91 months for the stable group). No cases were noted to have significantly improved over time using the same HRT TCA change criteria. Patient demographics in the stable and borderline groups (combined and considered stable) were similar. The stable/borderline group had 79%, 14%, and 7%, respectively, for Caucasian, Asian, and African American ancestry. The progressive group had 75%, 12.5%, and 12.5%, respectively, for Caucasian, Asian, and African American ancestry. Figures 1 to 4 show the distribution of IOP, CCT, DBP, and DPP by group. It can be seen (Figs. 1, 2) that IOP and CCT were not statistically different between groups and were thus likely relatively poor predictors of progression.

DBP was significantly lower in both the borderline and progressive groups compared to the stable group. DPP was significantly different between the three groups, with the

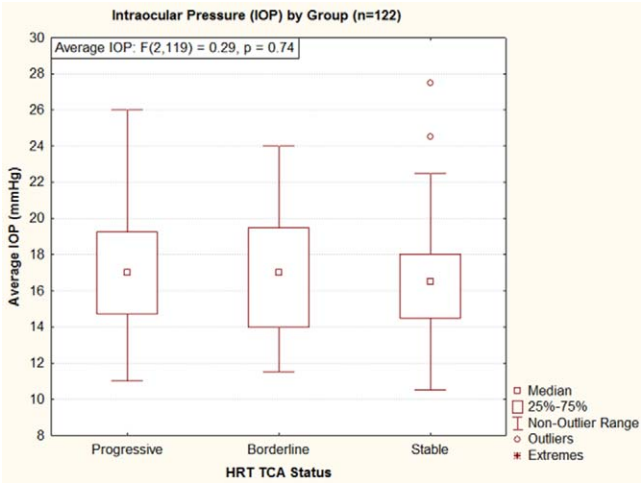


Figure 1. IOP for progression groups determined using HRT TCA outcome. There is no statistically significant difference between the groups. Interocular average of IOP was used because there was no significant inter-eye difference.

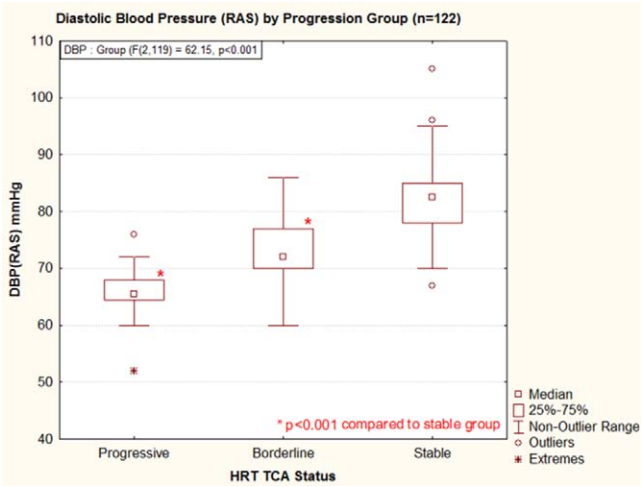


Figure 3. DBP (right arm sitting) for progression groups as determined using HRT TCA outcome. The stable group had significantly higher DBP compared to the borderline and stable groups. There was no statistical difference between the borderline and the progressive groups in terms of DBP alone.

progressive group having the lowest DPP (Fig. 4). Figure 5 shows DBP and DPP plotted by group, and Figures 6 and 7 show the relevant quantitative data.

ROC curve analysis (Figs. 8–10) and regression tree analysis (Fig. 11) were used to examine which predictor variables best separated group (i.e., stable, borderline, progressive). As can be seen from the ROC analysis, DBP and DPP were good predictors of grouping if one considers progressors (i.e., progression group) versus nonprogressors (i.e., stable and borderline groups). As can be seen from the ROC curves and regression analysis, DPP and DBP were statistically useful in determining correct grouping. IOP and CCT were not statistically useful in determining group.

Regression tree analysis, using the four predictors for classification (Fig. 11), shows that few misclassifications were made by using cutoffs of 56 mm Hg for DPP and 73 mm Hg for DBP. IOP and CCT did not provide any statistical assistance in predicting category.

To provide clinical illustrations in addition to the reported group data, HRT TCA and stereoparameter printouts are shown for the left eye of one of the progressive cases (female) for which an ambulatory 24-hour blood pressure profile was available (Figs. 12, 13; right eye showed similar trend). Pretreatment IOPs were in the range of 16 to 19 mm Hg in each eye, with the patient having a positive family history (mother), Raynaud's disease, and CCTs in the average range in each eye (560 μm range).

A significant nocturnal dip in DBP was seen in this patient, with the average nocturnal DBP being 50 mm Hg and the lowest DBP occurring at approximately 1 AM (37 mm Hg). The average DBP overall was recorded as 67 mm Hg. Looking at the nocturnal DBP, however, a realistic target IOP for this patient would be difficult (if not impossible) to define because DBP already averaged 50 mm Hg at night. This in essence represents a more challenging spectrum of glaucoma cases, the so-called "normal tension" glaucoma patients, who often continue to

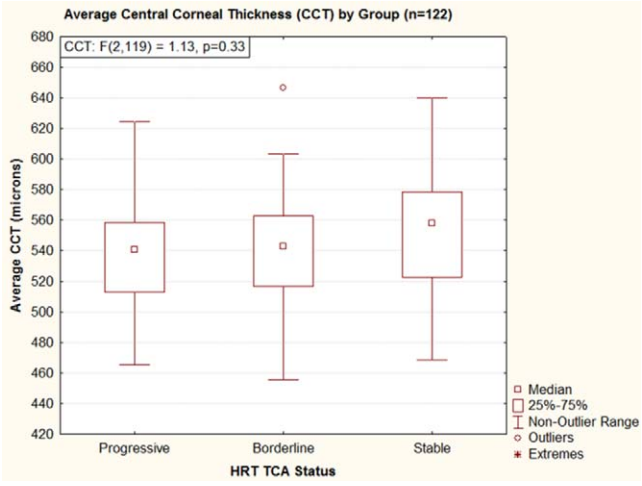


Figure 2. CCT for progression groups determined using HRT TCA outcome. There was no statistically significant difference between the groups in terms of CCT. Interocular average of CCT was used because there was no significant inter-eye difference.

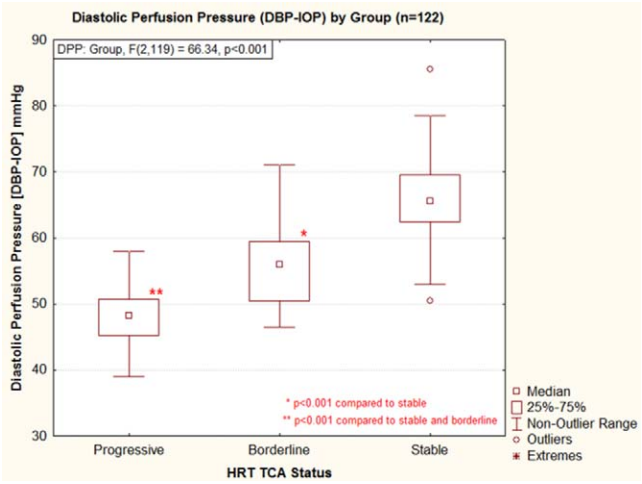


Figure 4. DPP for progression groups as determined using HRT TCA outcome. The stable group had significantly higher DBP compared to the borderline and stable group. The progressive group also showed a significantly lower DPP compared to both the borderline and stable groups.

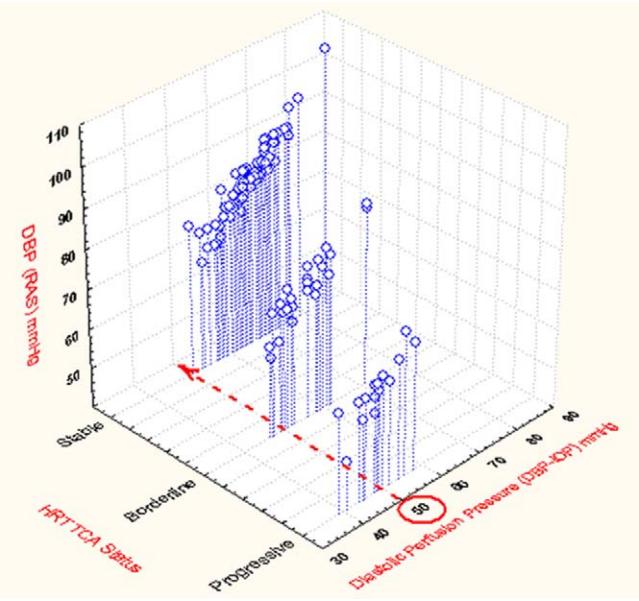


Figure 5. The relationship between diastolic perfusion pressure (DPP), DBP, and progression rates as determined using HRT TCA outcome. It can be seen that all patients in the stable group had a DPP of 50 mm Hg or greater.

exhibit progressive optic neuropathy despite low IOPs being attained therapeutically or surgically.

Discussion

Although there are differences in the study designs, the following studies have already found that lower DPP essentially equates to a higher risk for OAG: Baltimore Eye Study, Egna-Neumarket Study, Proyecto VER, Barbados Eye Study, and the Rotterdam Eye Study. It has also been shown in an Asian sample that lower DPP is associated with OAG.[17] The Barbados Eye Study[5] in particular showed that DPP under 55 mm Hg more than doubled the risk of OAG, a result supported by the findings in this study. Observations that decreased blood flow is found in OAG but not in ocular hypertensive patients with matched IOPs[24] are in line with the findings of this study because increased IOP with raised DBP could potentially result in adequate DPP. More recently, 24-hour ambulatory blood pressure profiles on 60 glaucoma patients showed an association between the degree of nerve fiber layer loss (using optical coherence tomography) and the time of day that hypertensive medication was administered (in the evening as opposed earlier in the day).[25] This effect was suggested to potentially arise from greater nocturnal dips in blood pressure when medications were taken later in the day. The authors of this report did not discuss image quality during image acquisition, a point that has been addressed in our study using HRT imaging.

The results presented in our paper agree with the previous reports of an increased risk of glaucomatous optic neuropathy associated with lower DPP. Our analyses suggest that a DPP of 56 mm Hg or lower is likely a reasonable clinical threshold for concern. This finding is in agreement with several studies

Table. Breakdown of Sex, Age, CCT, IOP, and DPP by HRT TCA grouping ($n = 122$)*

	Stable ($n = 82$)	Borderline ($n = 24$)	Progressive ($n = 16$)	Significance Level
% Female	62.17	54.17	75.00	
Mean IOP	16.75	17.27	17.19	$P = 0.74$
IOP SD	3.11	3.62	3.71	
Mean CCT	552.79	542.59	540.12	$P = 0.33$
CCT SD	38.34	42.19	36.52	
Mean DPP	65.78	55.61	48.44	$P < 0.01$
DPP SD	6.23	6.71	4.98	
Mean DBP	84.54	72.87	65.62	$P < 0.01$
DBP SD	6.28	6.31	5.39	
Mean age	65.43	59.35	62.58	$P = 0.87$
Age SD	11.81	14.04	10.47	

* As can be seen, DPP and DBP were found to be significantly different between groups.

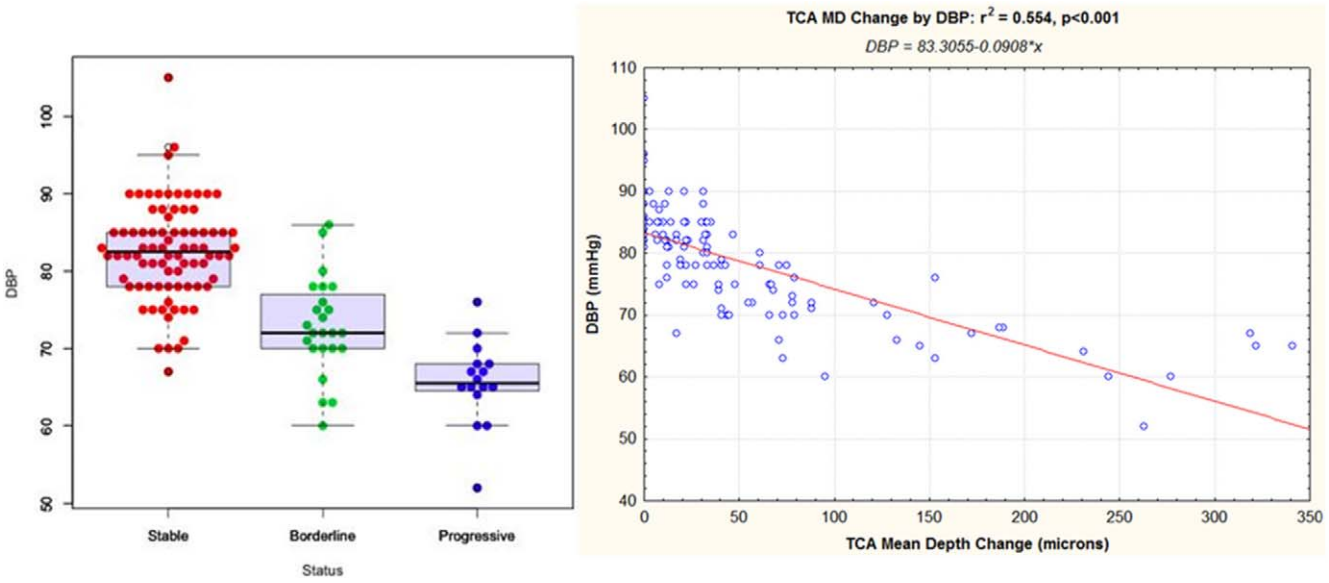


Figure 6. The relationship between DBP and TCA mean depth change (μm) of the largest cluster of pixels with statistically significant change within the optic disc as determined using HRT TCA. As can be seen, there is a significant coefficient of determination between DBP and TCA change ($P < 0.001$).

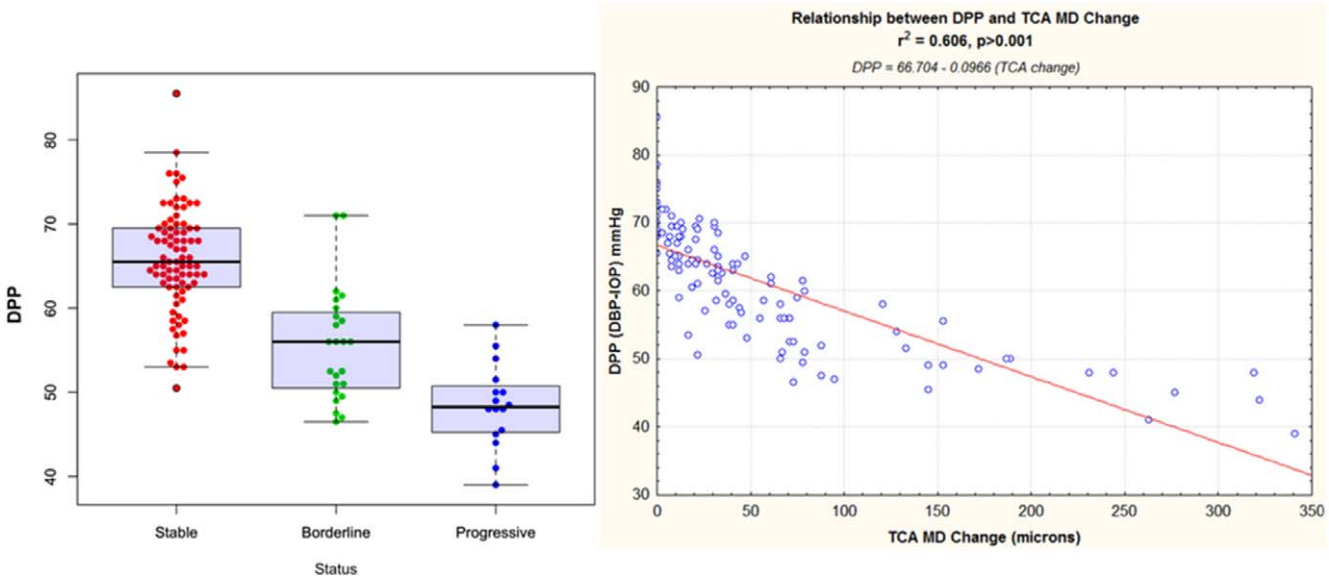


Figure 7. The relationship between DPP and TCA mean depth change (μm) of the largest cluster of pixels with statistically significant change within the optic disc as determined using HRT TCA. As can be seen, there is a significant coefficient of determination between DPP and TCA change ($P < 0.001$).

showing a 2- to 6-fold increased prevalence of OAG in patients with DPP lower than 55 mm Hg.[5,6,9,17] This research is novel, however, in that it is to our knowledge the first demonstration of increased progression rates with lower DPP using HRT TCA when the images were obtained using relatively stringent image acquisition criteria.

It is important to discuss briefly the reason for the use of a lower SD (20 μm) versus the 50 μm SD suggested as being acceptable in the HRT II manual. Although the limit of 50 μm SD is stated in the HRT manual and has been accepted in other peer-reviewed publications,[21] in our experience any HRT image with an SD greater than 25 to 30 μm results in clinically questionable fluctuations in stereoparameter trends and TCA data output. Once 30 μm is exceeded, even in the three-dimensional rendering of the optic nerve one can actually see the image degradation (i.e., the "bumpiness" of the three-dimensional rendering option). We suggest that a more conservative SD of 20 μm could be used, especially when looking for early glaucomatous change. It seems intuitive that the larger the SD in micrometers, the more change is required to detect progression; thus, selecting this lower SD cutoff provides for a more sensitive change criterion. Although we used change criteria based on a previous publication's guidelines,[22] we opted to use a more stringent criterion of

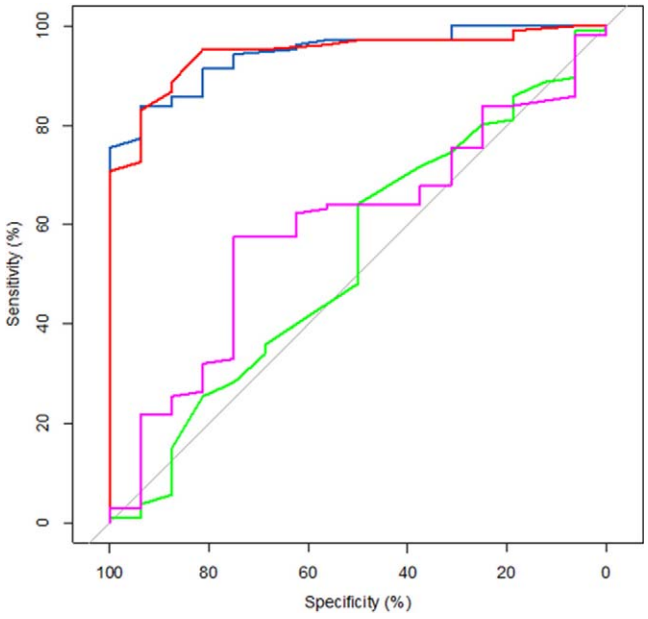


Figure 8. ROC analysis showing that DPP (*blue*) and DBP (*red*) show much better ability to predict grouping. This analysis compared essentially progressors (i.e., progression group) to nonprogressors (i.e., stable and borderline group). As can be seen, IOP (*green*) and CCT (*purple*) data were of no statistically significant use in determining group.

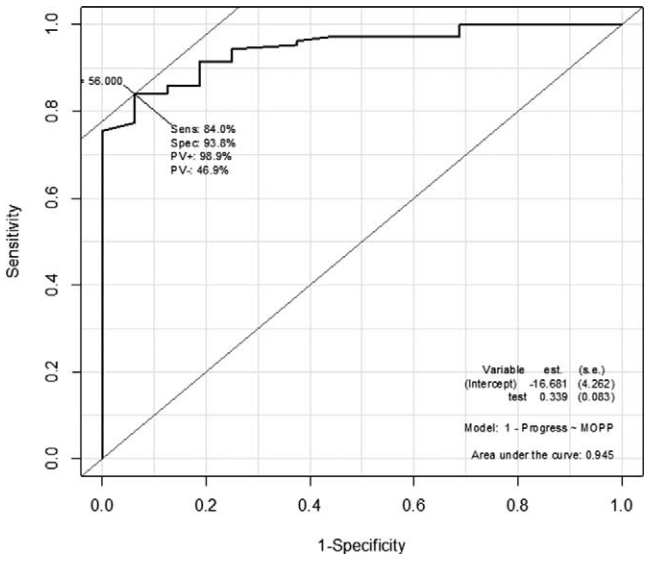


Figure 9. ROC analysis showing that DPP of 56 mm Hg gives the best separation of group when the progression group is compared to the other two groups (i.e., nonprogressors).

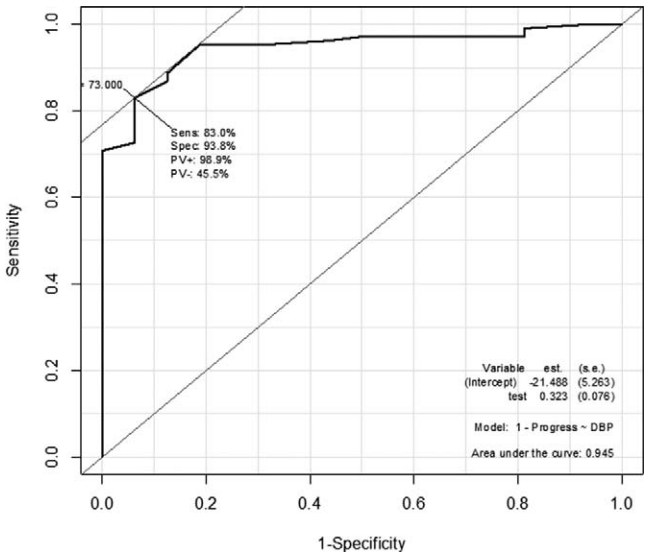


Figure 10. ROC analysis showing that DBP of 73 mm Hg gives the best separation of group when the progression group is compared to the other two groups (i.e., nonprogressors).

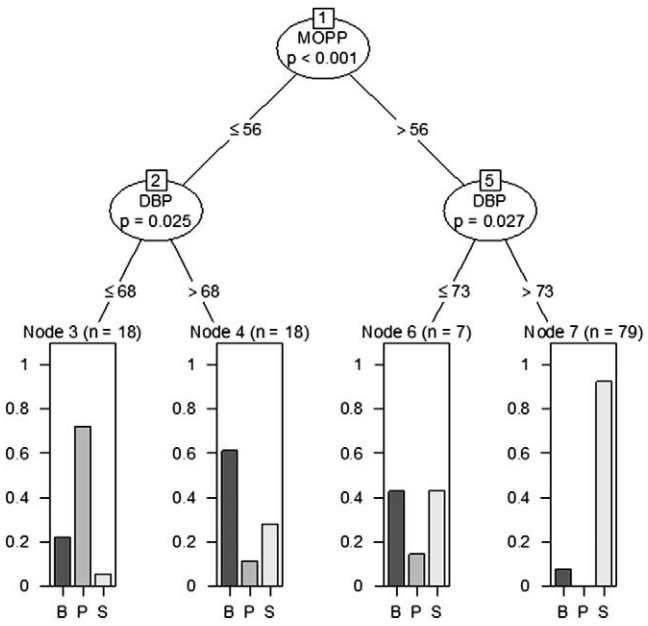


Figure 11. Regression tree analysis of the four predictors used in this study (i.e., DBP, DPP, CCT, and IOP). As can be seen, IOP and CCT do not provide any statistical assistance in separating the categories in the data, whereas DBP and DPP are statistically useful in separating categories correctly (B, borderline group; P, progressive group; S, stable group).

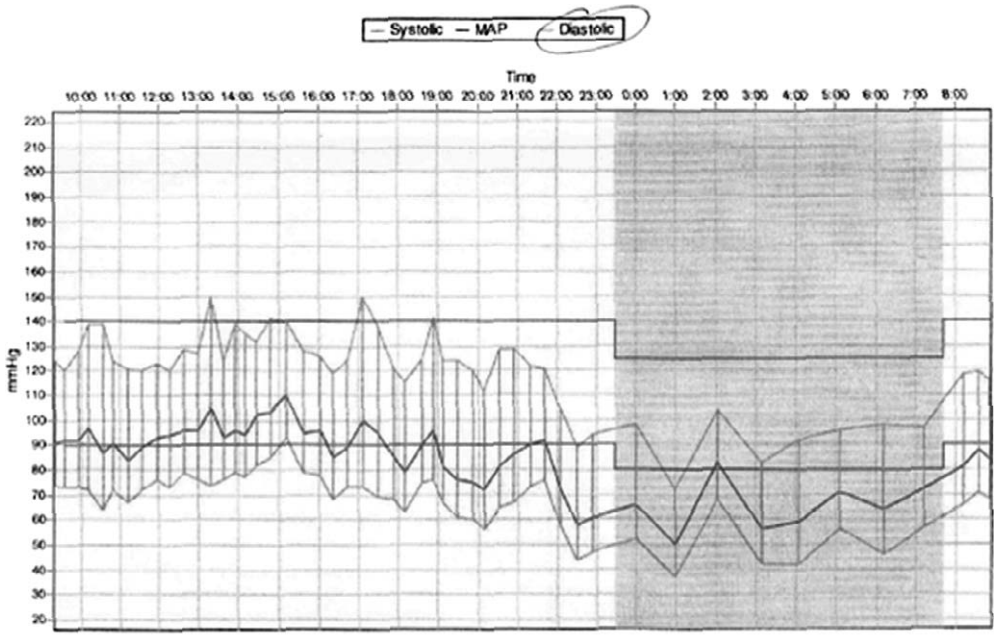
20 μm SD for imaging acquisition because reducing imaging noise will intuitively aid in more reliable progression detection.

When debating whether DPP should be examined closely or not, we should keep in mind that in the Barbados Eye Study,[5] the mean risk ratio was highest with "low perfusion pressure," with an almost three times higher relative risk (2.6 times) being reported. Compared to all other factors examined (age, approximately 1.1 times; family history, approximately 2.4 times; higher IOP, approximately 1.1 times; systolic blood pressure, approximately 0.8 times; and CCTs, approximately 1.4 times), this result agrees with the finding of our study that DPP may well be an important factor for classifying a patient as progressing. Therefore, from a clinical standpoint, a positive family history of a parent or sibling and a DPP of less than 56 mm Hg likely compose a reliable combination to predict progressive optic neuropathy. Of note, if a DPP of 56 mm Hg or lower is used as the risk factor, the relative risk of being in the progressive group with this risk factor present was 13.25 times (CI: 5.79–30.29 times, $P < 0.001$). It is thus likely that DPP of 56 mm Hg or less represents a relatively strong risk factor.

The DPP cutoff of 56 mm Hg suggested in our regression analysis is in agreement with a previous study[26] in which 24 healthy patients and 29 primary POAG patients had their 24-hour DPP profiles examined. None of the patients were on blood pressure medication, and the POAG group had ceased all topical glaucoma medications 1 month prior to the study. The average DPP of the control group was approximately 58 mm Hg, and the average DPP of the POAG group was 52 mm Hg. The similarity of these results is reassuring. This research concluded that the DPP was for the most part significantly different between the controls and the POAG group between the hours of midnight and 6 AM, a result that is very similar to the case from our study (Figs. 12, 13). To be clear, we did not get an ambulatory 24-hour blood pressure profile for any other patients, and this case may not be illustrative of the entire progressive group. Nonetheless, it is of interest that this profile from one of the progressive subjects in our study is very much in line with the trend observed in diagnosed POAG patients.[26]

The observation that DPP is a better indicator of progression than IOP supports the notion that NTG and OAG are in essence the same disease process, the only difference likely being the level of DBP (i.e., lower DBP in NTG cases) and the presence of autoregulation impairment. This point is reinforced by the observation that autoregulation has been shown to begin to become impaired at between 27 and 30 mm Hg in humans, consistent with the IOP levels at which we tend to see OAG present.[27] We are not suggesting that the low DPP is causative per se (although it appears to be a factor) because there is research to show that many patients have nocturnal dips in blood pressure and yet do not develop glaucoma.[26] Indeed in the previously mentioned study looking at 24 blood pressure profiles and 24-hour IOP trends, no significant difference was found between the controls and the POAG group in terms of "number of extreme dippers"; that is, >20% Dip, with "Dip" defined as [mean daytime DBP − (mean nocturnal DBP/mean daytime DBP)] × 100.[26] The notion that reduced DPP potentially impairs ocular blood blow in the absence of autoregulation has previously been suggested.[28,29] Whether autoregulation dysfunction is a cause or an effect of low DPP is a question outside the scope of this research, but given that a direct measure of autoregulation has proven very difficult,[16] DPP is likely a useful clinical parameter that clinicians can use to better identify patients at higher risk for progression.

Since perfusion is a function of two components and decreasing DBP can also decrease ocular perfusion, there are likely clinical ophthalmic complications associated with medical intervention for hypertension. Although the intervention may well be justified in terms of reducing cardiovascular risk, if our reported relationship is confirmed in larger scale studies, extra consideration should perhaps be extended to patients on glaucoma therapy or with ocular hypertension to ensure that perfusion pressures are not reduced to the point of creating excessive ischemia to the optic nerve, especially in those individuals with impaired autoregulation. Indeed, consistent with this notion is the observation that aggressive treatment of hypertension has been shown in some cases to cause serious damage to both the heart[30,31] and brain.[32] This point emphasizes the necessity for close collaboration between



General:	Overall:	Awake:	Asleep:
Nr. measurements	51	43	8
Total time	11:34:00 PM	3:21:00 PM	8:13:00 AM
Average	120 / 67 mmHg	125 / 71 mmHg	93 / 50 mmHg
SD	16.9 / 11.9 mmHg	12.2 / 9.0 mmHg	10.3 / 10.2 mmHg
Pulse Pressure	52.7 mmHg	54.6 mmHg	42.5 mmHg

Figure 12. Twenty-four-hour ambulatory blood pressure profile printout of one of our progressive cases (female) obtained 1 week after the last HRT scan. The pretreatment IOPs were in a range of 17 to 19 mm Hg in each eye, CCTs were average (563 μm OD and 558 μm OS), and there was a positive family history (mother) and Raynaud's. It can be seen that there was a moderate drop in DBP at night with the average "asleep" DBP being 50 mm Hg. The blood pressure trend of this patient agrees well with the overall results of this study in that a lower DBP appears to be a strong predictive risk factor for progressive optic neuropathy.

eye care providers and primary care physicians regarding the patient's DBP in the overall management of glaucomatous optic neuropathy. The data presented in this paper suggest that a DPP of approximately 56 mm Hg is likely a demonstrably useful clinical threshold. Larger studies will likely aid in refining this range, but if confirmed, it will allow eye care providers to set target therapeutic IOPs with a much greater degree of confidence (with DBP in mind) for patients ultimately diagnosed with glaucoma as evidenced by progressive optic neuropathy. Since these individuals also likely have a high risk of autoregulation impairment,[28,29] this approach appears justified.

Of interest, a study[33] published in 1942 examining the relationship between a "diastolic co-efficient" (DBP/IOP) and severity of visual field loss found a significant association between lower diastolic ratios and patients with more severe visual field loss. Figure 14 (replotted using the published raw data) shows that there is indeed a significant trend of worsening visual field status with a lower diastolic coefficient, a finding that agrees well with our HRT TCA results. It is to the credit of the authors of this 1942 paper that their finding of increased visual field damage with lower DPP is supported via HRT TCA 70 years later.

The results presented in this study raise an intriguing question with respect to other neurodegenerative conditions. It has been suggested in the literature that patients with neurodegenerative diseases with apoptotic cell death (such as Alzheimer's disease and Parkinson's disease) may have optic nerve fibers that appear to be less resistant to increases in IOP.[37] The frequency of NTG in particular also appears to be somewhat greater with these neurodegenerative conditions.[37] Although beyond the scope of this research, the results of our study raise an intriguing possibility as to whether a similar low perfusion pressure issue exists in patients with Alzheimer's disease and dementia. Although treatment of hypertension is important in terms of preventing fatal cardiovascular conditions, all homeostatic mechanisms in the body have an ideal range for optimal function, with blood pressure likely being no different. If this research is confirmed on a larger scale using identical image quality control criteria, hypoperfusion of neuronal tissue has likely been underemphasized in the medical literature and it would seem logical to look at other progressive neurological diseases associated with glaucoma in a similar light. Although controversial, it is certainly of interest to note that hypertension actually appears to be a protective factor in glaucoma in some epidemiological studies.[34–36] Potential drawbacks of this study are the relatively small sample size overall and the relatively low number of progressive cases identified in the patient files (mainly due to the relatively strict inclusion criteria). There is also a risk of type II error in the comparisons between the groups, which showed nonsignificant differences (i.e., CCT and IOP). The strict inclusion criteria were chosen in order to extract clinically meaningful data with as little noise as possible in the imaging data acquired. In the UWSO HRT clinic service, it is not unusual to see 60% to 70% of referred patients ultimately

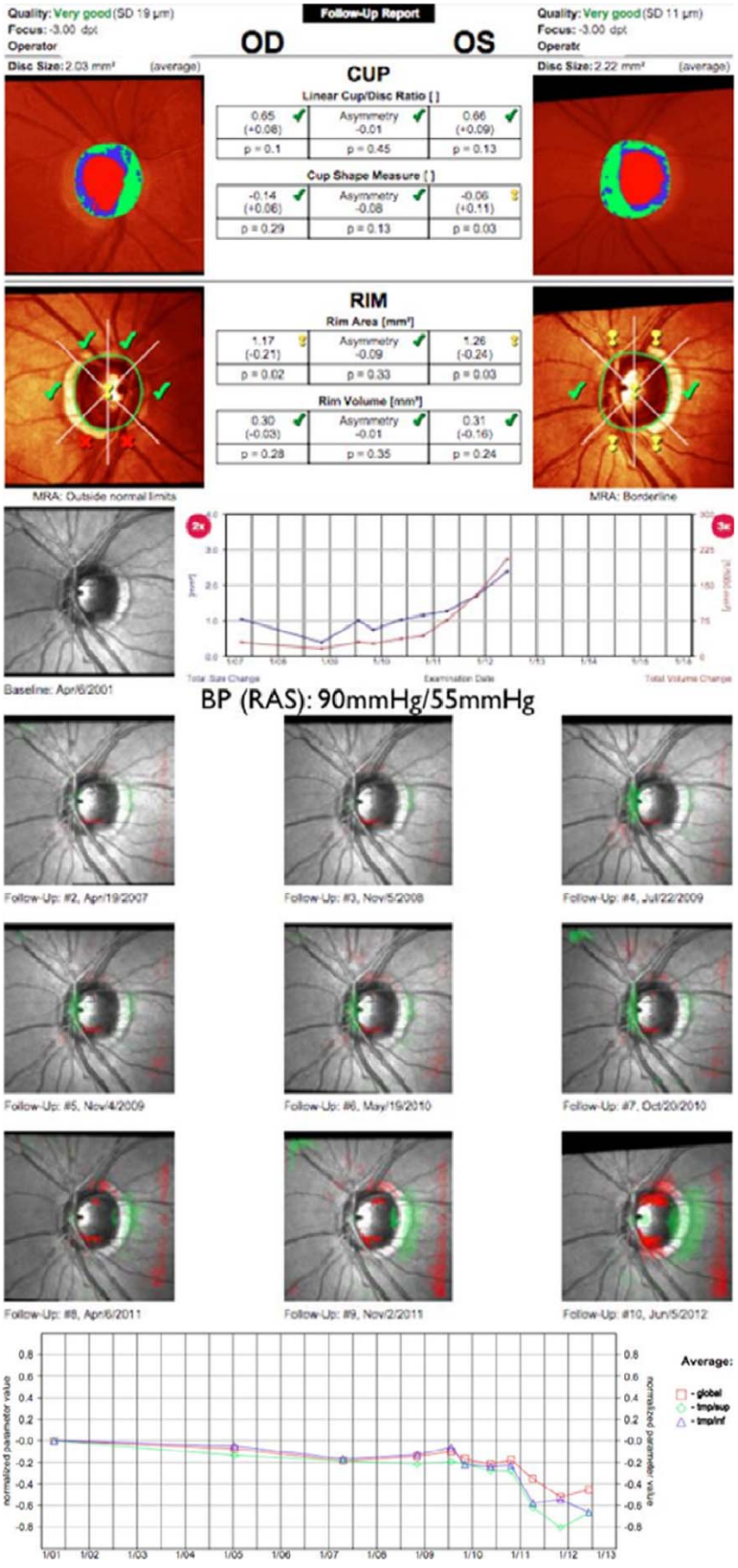


Figure 13. Main printout and OS stereotrend and TCA data for a female patient in the progressive group (OD was similar). The HRT data shown is for the same patient whose ambulatory 24-hour blood pressure profile was made available to us within 1 week of the last HRT scan. The data used in this paper were the last DBP measurement at the last HRT session included in the analysis. The 24-hour ambulatory blood pressure profile for this patient was obtained as other testing was ongoing with the family physician to investigate unexplained fainting episodes. As can be seen, the blood pressure measurement at the last HRT session was 90/55 mm Hg (right arm sitting), which is in good agreement with the ambulatory 24-hour data (patient awake section, see Fig. 7).

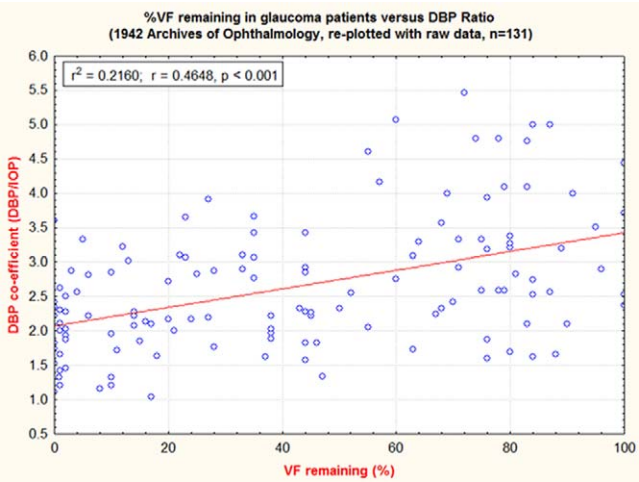


Figure 14. Data replotted from a 1942 paper[33] reporting the relationship between severity of visual field (VF) loss and DBP in relation to IOP (expressed as a DBP coefficient). It can be seen that there is a significant association between more severe VF loss and a lower DBP coefficient. This observation is in agreement with the increased progression rate of progressive optic neuropathy observed in this study using quantitative and objective HRT data.

be discharged, with one of the most common referral reasons being, for example, asymmetric disc size (misinterpreted as asymmetrical cupping) or alternately a simple anomalous optic nerve. Looking at other large-scale studies such as the Barbados Eye Study,[5] the relative percentage of progressors in comparison with all patients examined was similar at 10% to 15%. Thus, the proportion of progressors relative to the total sample size in this study is reasonably reflective of the UWSO HRT service.

Imaging, like any clinical measure, is only as good as its signal-to-noise ratio and this point needs to be emphasized clinically. Objective imaging such as that used in the HRT is becoming more widespread in the clinical management of OAG and thus accordingly, we must be vigilant regarding the quality of the data used to make clinical interpretations regarding our patients and not simply rely on manufacturer's guidelines. HRT imaging is to our knowledge the only imaging device to report quantitatively the actual SD of the image acquired in micrometers. Ultimately, quantitative criteria for topographic change can only be agreed upon clinically when this change criterion also takes the noise level of the image attained into account.

In summary, the findings of this study show that lower levels of DPP are associated with a greater degree of progression as measured using HRT TCA criteria. These results likely warrant consideration of a larger scale study. Our study suggests that a DPP of 56 mm Hg or lower appears sensible in terms of potentially identifying patients at relatively higher risk of progressive optic neuropathy. Although the practicality of raising blood pressure in "maximally IOP treated" patients (i.e., NTG) has been questioned,[38] the notion of at least being aware of the blood pressure level and using this measure to determine target IOPs is in line with suggestions in other publications.[17,39,40] However, given the confounding factor of impaired autoregulation, raising blood pressure likely remains an option that should only be considered in patients with low nocturnal DPP and DBP and rapidly progressing glaucoma despite maximally treated IOP who have no other treatment options. At the very least, calcium channel blockers should likely be avoided in OAG patients,[16] with either diuretics or beta-blockers being considered in lieu of them if blood pressure medication is required. This is justified on two fronts. First, an increased risk of glaucoma with calcium channel blocker use has been shown,[16] and second, suppression of the autoregulatory response has been shown with the use of calcium channel blockers.[41] The importance of monitoring blood pressure and not "overtreating" hypertension has also been mentioned elsewhere in terms of avoiding low perfusion pressures in diagnosed OAG cases.[17]

This research represents a significant step forward in confirming the relationship between lower perfusion pressure and increased progression rates in OAG using relatively stringent imaging criteria. In light of these findings, OAG patients placed on blood pressure–lowering medications may require their target DBP to set with their treated IOP levels kept in mind to maintain adequate optic nerve perfusion levels, while still minimizing any cardiovascular concerns of the primary care physician.

Acknowledgments

The authors thank David Williams (University of Waterloo School of Optometry & Vision Science) and two anonymous reviewers for valuable comments in the preparation stages of this manuscript.

References

1. Resnikoff S, Pascolini D, Etya'ale D, et al. Global data on visual impairment in the year 2002. *Bull World Health Organ*. 2004; 82:844–851.
2. Quigley HA. Number of people with glaucoma worldwide. *Br J Ophthalmol*. 1996;80:389–393.
3. Quigley HA, Broman AT. The number of people worldwide with glaucoma in 2010 and 2020. *Br J Ophthalmol*. 2006;90: 262–267.
4. Majeed F, Tauheed S, Aamir IS, Atif A, Majeed R. Frequency of normal tension glaucoma in suspected cases of primary open angle glaucoma. *Pak J Ophthalmol*. 2007;23:192–197.
5. Leske MC, Wu SY, Hennis A, Honkanen R, Nemesure B. Risk factors for incident open angle glaucoma (Barbados Eye Studies). *Ophthalmology*. 2008;115:85–93.
6. Zheng Y, Wong TY, Mitchell P, Friedman D, He M, Aung T. Distribution of ocular perfusion pressure and its relationship with open angle glaucoma: the Singapore Malay Eye Study. *Invest Ophthalmol Vis Sci*. 2010;51:3399–3404.
7. Sommer A, Tielsch JM, Katz J, et al. Relationship between intraocular pressure and primary open angle glaucoma among white and black Americans. The Baltimore Eye Study. *Arch Ophthalmol*. 1991;109:1090–1095.
8. Leske MC. Ocular perfusion pressure and glaucoma: clinical trial and epidemiological findings. *Curr Opin Ophthalmol*. 2009;20:73–78.

9. Leske MC, Heijl A, Hyman L, Bengtsson B, Dong L, Yang Z. Predictors of long term progression in the early manifest glaucoma trial. *Ophthalmology*. 2007;11:1965–1972.
10. Kitazawa Y. Normal tension glaucoma: inaugural scientific meeting of the SEAGIG Group. *Asian J Ophthalmol*. 2001;3: 14–17.
11. Finucane MM. National, regional and global trends in body mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants. *The Lancet*. 2011;377:557–567.
12. Dielemans I, Vingerling JR, Algra D, Hofman A, Grobbee DE, de Jong PT. Primary open angle glaucoma, intraocular pressure, and systemic blood pressure in the general elderly population: the Rotterdam Eye Study. *Ophthalmology*. 1995; 102:54–60.
13. Gordon MO, Beiser JA, Brandt JD, et al. The ocular hypertension study: baseline factors that predict the onset of primary open angle glaucoma. *Arch Ophthalmol*. 2002; 120:714–720.
14. Collingnon N, Dewe W, Guillaume S, Collignon-Brach J. Ambulatory blood pressure monitoring in glaucoma patients. The nocturnal systolic dip and its relationship with disease progression. *Int Ophthalmol*. 1998;22:19–25.
15. Graham SL, Drance SM. Nocturnal hypotension: role in glaucoma progression. *Surv Ophthalmol*. 1999;43(S1);S10–S16.
16. Grover DS, Budenz DL. Ocular perfusion pressure and glaucoma. *Int Ophthalmol Clin*. 2011;51:19–25.
17. He Z, Vingrys AJ, Armitage JA, Bui BV. The role of blood pressure in glaucoma. *Clin Exp Optom*. 2011;94:133–149.
18. Sommer A, Tielsch J. Blood pressure, perfusion pressure and open angle glaucoma. *Arch Ophthalmol*. 2008;126:741–742.
19. Kim JH, Kang SY, Kim NR, et al. Prevalence and characteristics of glaucoma among Korean adults. *Korean J Ophthalmol*. 2011;25:110–115.
20. August P. Hypertension in men. *J Clin Endocrinol Metab*. 1999;84:3451–3454.
21. Ramdas WD, Wolfs RCW, Hofman A, de Jong PT, Vingerling JR, Jansonius NM. Heidelberg retina tomograph (HRT3) in population-based epidemiology: normative values and criteria for glaucomatous optic neuropathy. *Ophthalmic Epidemiol*. 2011;18:198–210.
22. Chauhan BC, Hutchison DM, Artes PH, et al. Optic disc progression in glaucoma: comparison of confocal scanning laser tomography to optic disc photographs in a prospective study. *Invest Ophthalmol Vis Sci*. 2009;50:1682–1691.
23. Chauhan BC, LeBlanc RP, McCormick TA, Rogers JB. Test-retest variability of topographic measurements with confocal scanning laser tomography in patients with glaucoma and control subjects. *Am J Ophthalmol*. 1994;118:9–15.
24. Kerr J, Nelson P, O'Brien C. A comparison of ocular blood flow in untreated primary open angle glaucoma and ocular hypertension. *Am J Ophthalmol*. 1998;126:42–51.
25. Krasińska B, Banach M, Karolczak-Kulesza M, Krasiński Z, Głuszek J, Tykarski A. Observations on degenerative changes within the optic nerve in patients with primary open glaucoma and arterial hypertension: 6 month follow up. *J Clin Hypertens (Greenwich)*. 2012;14:701–710.
26. Costa VP, Jimenez-Roman J, Gil Carrasco F, Lupinacci A, Harris A. Twenty-four-hour ocular perfusion pressure in primary open angle glaucoma. *Br J Ophthalmol*. 2010;94:1291–1294.
27. Riva CE, Grunwald JE, Petrig BL. Auto-regulation of human retinal blood flow. An investigation with laser Doppler velocimetry. *Invest Ophthalmol Vis Sci*. 1986;27:1706–1712.
28. Flammer J, Mozaffarieh M. What is the present pathogenetic concept of glaucomatous optic neuropathy? *Surv Ophthalmol*. 2007;52:162–173.
29. Hayreh SS. Blood flow in the optic nerve head and factors that may influence it. *Prog Retin Eye Res*. 2001;20:595–624.
30. Cruickshank JM, Thorp JM, Zacharias FJ. Benefits and harm of lowering high blood pressure. *Lancet*. 1987;1:581–584.
31. Somes GW, Pahor M, Shorr RI, Cushman WC, Applegate WB. The role of diastolic blood pressure when treating isolated systolic hypertension. *Arch Intern Med*. 1999;159: 2004–2009.
32. Voko Z, Bots ML, Hofman A, Koudstaal PJ, Witteman JC, Breteler MM. J-shaped relation between blood pressure and stroke in treated hypertensives. *Hypertension*. 1999;34:1181–1185.
33. Reese AB, McGavic JS. Relation of field contraction to blood pressure in chronic primary glaucoma. *Arch Ophthalmol*. 1942;27:845–850.
34. Bonomi L, Marchini G, Marraffa M, Bernardi P, Morbio R, Varotto A. Vascular risk factors for primary open angle glaucoma: the Egna-Neumarket Study. *Ophthalmology*. 2000; 107:1287–1293.
35. Costa VP, Arcieri ES, Harris A. Blood pressure and glaucoma. *Br J Ophthalmol*. 2009;93:1276–1282.
36. Mitchell P, Lee AJ, Rochtchina E, Wang JJ. Open-angle glaucoma and systemic hypertension: the Blue Mountains Eye Study. *J Glaucoma*. 2004;13:319–326.
37. Bayer AU, Keller ON, Ferrari F, Maag KP. Association of glaucoma with neurodegenerative disease with apoptotic cell death: Alzheimer's disease and Parkinson's disease. *Am J Ophthalmol*. 2011;133:135–137.
38. Caprioli J, Coleman A. Perspective: blood pressure, perfusion pressure and glaucoma. *Am J Ophthalmol*. 2010;149:704–712.
39. Schmidl D, Garhofer G, Schmetterer L. The complex interaction between ocular perfusion pressure and ocular blood flow: relevance for glaucoma. *Exp Eye Res*. 2011;93: 141–155.
40. Delaey C, Van de Voorde J. Pressure-induced myogenic responses in isolated bovine retinal arteries. *Invest Ophthalmol Vis Sci*. 2000;41:1871–1875.
41. Demailly P, Cambien F, Plouin PF, Baron P, Chevallier B. Do patients with low tension glaucoma have particular cardiovascular characteristics? *Ophthalmologica*. 1984;188:65–75.