PASCAL TONOMETRY: OCULAR PULSE AMPLITUDE AS IT RELATES TO MEAN OCULAR PERFUSION PRESSURE

by

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Has been approved

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ABSTRACT

Purpose: To investigate the validity of the ocular pulse amplitude (OPA) using the Pascal dynamic contour tonometer (DCT) in a healthy population. Previous studies, considered the choroidal perfusion, which is indirectly measured by OPA, as a method that could be established as an independent risk factor in primary open angle glaucoma (POAG). Pulsatile blood flow into the eye causes a rhythmic fluctuation of the steady-state intraocular pressure (IOP). Ocular pulse measurements primarily reflect the difference between the systolic and diastolic blood pressure in the choroidal vascular bed.

Methods. Twenty five young healthy subjects were recruited for participation. Both eyes were selected for measurement of data. The study was approved by the Human Subjects Review Committee at Ferris State University. OPA and IOP was measured using the Pascal DCT. MOPP was obtained using the formula, MOPP = 2/3 [DBP + 1/3 (SBP – DBP)] – IOP, from Sehi, et al. The subjects' systolic and diastolic blood pressures were measured on the left arm, using the sphygmomanometer. The IOP used to calculate MOPP was measured by Goldmann applanation tonometry (GAT).

Results. Pearson's correlation coefficient of OPA and MOPP, which was R =0.231, was determined. It shows a low positive correlation and is not statistically significant. According to both Pearson's correlation coefficient and the paired samples t-test, there was a moderate positive correlation between GAT IOP and DCT IOP. However, despite the statistical significance (R = 0.492), there is a statistically significant difference in their means (P =0.032). This suggests that DCT data is not interchangeable to the GAT data, and one measurement cannot substitute for the other.

Conclusion. Overall, the results from this study have provided additional evidence that OPA cannot be considered an independent risk factor for glaucoma, such that there is no relationship between the OPA value and the MOPP in a normal population.

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INTRODUCTION

Role of cornea biomechanics has invariably shown to have a relationship on the effect of intraocular pressure measurement in the management of glaucoma. Current research suggests that this may not only implicate glaucoma management as more accurate intraocular pressure measurement methods are developed, but also redefine corneal biomechanics and its influence of lamina cribosa biomechanics. The biomechanics of the cornea may also have a role as an indicator of overall globe biomechanics.[1] Thus, this understanding of corneal biomechanics between individuals may explain why some optic nerve heads are more susceptible to damage by variations in IOP.[1] The primary structural component of the cornea and sclera is collagen, which provides a resilient, protective coat to the globe.[1] Contained primarily in Bowman's layer and the stroma, collagen has a high tensile strength and constitutes 90% of the total thickness of a hydrated cornea.[1] The cornea is highly organized into 300 collagen fibrils centrally, which are held in a matrix of proteoglycans that maintains uniform, inter-fibrillar spacing.[1] The number of fibrils increases to around 500 at the limbus. As a result of the physiology and biochemical nature of collagen and its proteoglycan matrix, the human cornea has variable thickness, and displays different physical properties when stress is applied in different directions.[1] These properties of corneal biomechanics are not constant: they change with advancing age; they are altered with level of hydration; and they progressively result in a loss of stromal lamellae organization.[1]

Two landmark studies provide the basis of this research, in which the aim is to identify any relationship between the mean ocular perfusion pressure (MOPP)

and ocular pulse amplitude (OPA) provided by the Pascal dynamic contour tonometer. It has been proposed that vascular risk factors are among the major precipitating factors that lead to the development of glaucomatous optic neuropathy.[2] Blood flow in any tissue is generated by the perfusion pressure which is defined as the difference between mean arterial blood pressure (MAP) and venous pressure. In the resting position MAP is calculated as:

$$MAP = DBP + 1/3\ (SBP - DBP)^{2,3,4}$$

It is also found that the difference between the systolic (SBP) and diastolic blood pressure(DBP) is the pulse pressure.[2] In the eye, the venous pressure should be marginally higher than the intraocular pressure (IOP), to allow for adequate blood circulation.[2] Therefore, for the calculation of the mean ocular perfusion pressure (MOPP), IOP is substituted for venous pressure.[2,3,4,5,6,] and the MOPP in the eye is equal to the difference between the MAP and IOP.[2,3,7,8,9]

$$MOPP = 2/3[DBP + 1/3(SBP - DBP)] - IOP^{2,3,7,8,9}$$

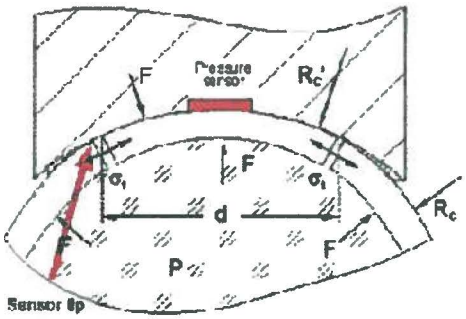
Maryl, et al., studied many variables including scanning laser Doppler flowometry, laser interferometric measurement of fundus pulsation, visual field testing, and non-invasive measurement of systemic hemodynamics, with the goal of discovering evidence that ocular blood flow abnormalities are involved in the pathogenesis of glaucoma and hemodynamic effects of current anti-glaucoma drugs.3 Mayrl, et al., confirmed that there is an abnormal association between blood pressure and ocular perfusion in patients with primary open-angle glaucoma or ocular hypertension and since has conducted research investigating the ocular hemodynamic effects of dorzolamide and timolol.[3]

Since the development of the dynamic contour tonometer (DCT) (Pascal; Swiss Microtechnology AG, Port, Switzerland) in 2003, many comparative studies have been completed between both normal and glaucomatous subjects. As a method of measuring IOP without the influence of corneal thickness, DCT has been researched in many facets of glaucoma research. The DCT instrument contains a contoured tip designed to fit the corneal surface and compensates for any corneal forces while measuring IOP with its pressure sensor.[10] It represents a novel technique because unlike Goldmann applanation tonometry (GAT) and other applanation methods, it is not affected by central corneal thickness (CCT).[10,11] Based on the working principles of DCT, matching up the concave pressure sensor with the cornea provides direct measurements independent of corneal properties, such as corneal curvature, corneal elasticity and corneal thickness. The continuous measurement of IOP is based on the direct trans-corneal pressure detection of a chip that is embedded within the contact tonometer, which closely resembles the corneal contour, thus minimizing the amount of corneal deformation.[12] The sensing chip allows for simultaneous measurement of ocular pulse amplitude (OPA).[10,11,12]

The OPA is an indirect indicator of the choroidal perfusion and reflects the ocular blood flow corresponding to the heart pulse as a function of time.[12] Previously, there has been questionable evidence that the OPA could play a role in the clinical course of glaucoma because a reduction of the blood flow to the retinal layers may be related to hypoxia and further cell death, attributed to the nerve fiber loss in glaucoma.[12] The key to the DCT technology is that the

surface-independent measurement of pressure can be achieved when a hypothetical corneal contour is matched by the contour of the Pascal tip.[12]

Figure 1: Diagram of contour-matched pressure-sensing tip of DCT applied to the corneal surface. Opposed to forceful applanation, the DCT tip closely matches corneal shape and tangential forces are theoretically neutralized.



The force distribution , which is needed to gently fit the corneal surface to the hypothetical contour, counterbalances the force distribution generated by the IOP.[12] The distribution of interface forces between the tip and the cornea equals the force distribution generated by the IOP.[12]

The objective of this study is to determine if there is positive correlation of the OPA from the Pascal DCT to the MOPP measured through systemic blood pressure and IOP in a normal healthy population. Conclusions from this pilot study could offer evidence to affirm or refute Swiss Microtechnology's claim that the Pascal DCT may provide an independent risk factor for glaucoma. This study provides baseline data about hemodynamic parameters in the normal subjects, which may provide insight to the known reduced choroidal and optic nerve head blood flow in glaucomatous patients. Furthermore, by taking another look at the controversial significance of the OPA provided by the DCT, it may offer opportunity for a newer concept that may develop into an additional clinical method by which practitioners can manage glaucoma and ocular

hypertension. Finally, considering previous studies, it is proposed that there is no relationship between the OPA value provided by the DCT and the hemodynamic blood flow to the optic nerve head. The aim of this pilot research is to provide data in order to conduct more elaborate studies comparing the normal population to an ocular hypertensive population and primary open angle glaucoma population. A secondary aim of this study is to re-evaluate at the comparison of the IOP measurement of DCT and the IOP measurement obtained by GAT and a correction factor of central corneal thickness.

Glaucoma is the second leading cause of blindness in the world. Approximately 67 million people have glaucoma and of those, approximately 7 million are bilaterally blind from the disease.[13] In 2000, approximately 150,000 people in the United States were blind from glaucoma in.[13] The epidemiology of primary open angle glaucoma in U.S., Europe, and Australia shows that 75-95% of glaucoma in Caucasians is primary open angle (POAG). The total loss and societal costs are unknown because the visual impairment outcome of glaucoma is so broad. The effects range from loss of peripheral vision, loss of depth perception, loss or reduction of contrast sensitivity, and loss of sight.[13]

Materials and Methods

To conduct this study, 25 healthy subjects were recruited. These control subjects were defined as in good general health by the following exclusions: diagnosed with hypertension, diagnosed with Type I or Type II diabetes mellitus, diagnosed with primary or secondary glaucoma, taking diuretics, taking any medications to treat any vascular perfusion disease, anemia, or clotting

disorders. There were 12 males and 13 females ranging in age from 22-32, with a single subject who was 55.

The measurement of systemic blood pressure, Goldmann applanation tonometry (GAT), Pascal dynamic contour tonometry (DCT), central corneal thickness (CCT) were all collected in a randomized order. However, GAT applanation and CCT measurement were separated by a time of five minutes in order to prevent the corneal thickness measurement from being influenced by applanation. The CCT measurement was made using high frequency ultrasonic pachymetry (Pachette; DGH 5100E, Philadelphia, PA). Five measurements of the central corneal were measured and averaged.

Ultrasound pachymetry employs ultrasonic bursts to reflect off the back surface of the cornea and correlates the thickness of the cornea with the time taken for the reflected wave to return to its source.[14,15,16] Ultrasound pachymetry uses a transducer probe that emits high frequency sound wave pulses that are reflected from the front and back surfaces of the cornea. A sensor measures the time difference between the two pulse signals. The corneal thickness was then calculated by multiplying this time delay by the velocity of sound in the human cornea.[14,15,16] The velocity of sound throughout the cornea has been determined to be 1640 m/s.[15,16]

Prior to GAT, one drop of Fluress (0.25% fluorescein sodium and 4% benoxinate hydrochloride ophthalmic solution) was instilled into each eye, and prior to DCT, one drop of 0.50% proparacaine hydrochloride solution was instilled into each eye. The IOP correction model for central corneal thickness (CCT) by

Phillip E. Walling was used to calculate IOP using GAT.[17] The following formula was used:

$$P = A + (550 - T)/18e^{-0.005A}$$

where P = calculated IOP using corneal thickness

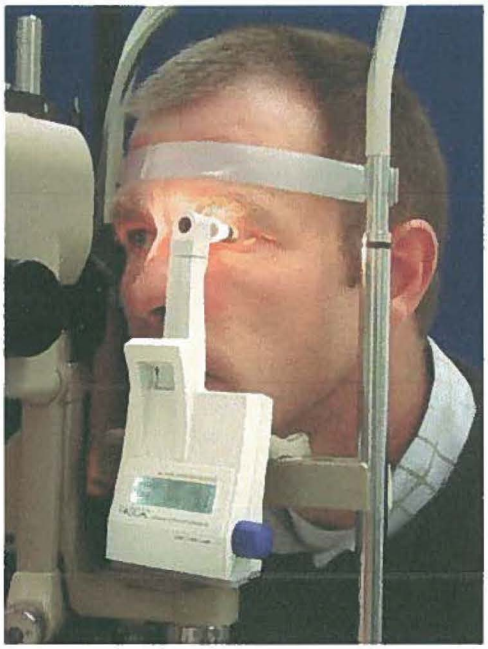
A = GAT reading in millimeters of Mercury (mm Hg)

T = CCT in micrometers (μm)

$18e^{-0.005A}$ = correction factor for nonlinear relationship between high measured IOP with GAT and increased corneal thickness

The DCT was mounted onto a GAT stand. A sterile disposable sensor tip cover was installed to the sensor tip and the device was centered onto the subject's cornea. Correct positioning of the tip was indicated by an audible signal that changed in pitch with each detected change in pressure. The tip generated an electric signal and rhythmic oscillations corresponding to the pressure signal, detected during 6-10 heartbeats. Pressure readings were sampled at 100 Hertz (Hz) and transferred to a micro processor-based control unit that computed and presented the IOP measured. The OPA value was displayed on the digital screen in units of mm Hg. The quality score, Q, ranged from excellent, 1, to poor 4-5. Only scores of 1 and 2 were accepted in this study. The measurement was repeated until a quality score of either 1 or 2 was obtained. With all subjects, the measurement was taken at least twice for repeatability.

Figure 2: Diagram of dynamic contour tononomer installed onto slit-lamp, demonstrating proper technique of measurement



Procedure

Two separate stations were organized for data collection. At Station 1 systemic blood pressure and GAT were measured, in that order. Blood pressure was taken on the left arm in the sitting position with a Heine sphygmomanometer. At Station 2 DCT and ultrasound pachymetry were measured. The order of the measurement was not randomized at this station, due to the time delay between GAT and ultrasound pachymetry. A five minute delay between GAT and ultrasound pachymetry was intended to reduce tonographic effects. However, the order of Station 1 and Station 2 was randomized among all the subjects.

Results

Bivariant correlations (Pearson correlation coefficients) and linear regression analyses were performed to ascertain the presence of a linear relationship between parameters of IOP/MAPP and OPA. A paired sample t-test was used for the analysis of measurement differences between the methods.

Bland-Altman analysis was used to evaluate pressure dependency of the difference between the methods. Mean difference and 95% limits of agreement were calculated for GAT and DCT measurements. Linear regression analysis was used to determine the associations between GAT and DCT differences, along with CCT.

Table 1: Bland-Altman Analysis of the Data

	N	Minimum	Maximum	Mean	Std.dev.	Skewness	Kurtosis
GAT IOP	50	9.0	20.0	14.74	2.47	-.245	0.053
DCT IOP	50	10.8	19.9	15.48	2.08	0.091	-0.280
OPA	50	1.0	4.0	1.97	0.71	0.820	0.671
CCT	50	483.0	649.0	552.6	37.6	0.470	0.183
IOP(corr)	50	7.1	20.9	14.6	3.28	-0.332	-0.466
MOPP	50	38.1	56.5	48.0	5.1	-0.136	-0.923

Pearson's Correlation Coefficient for DCT and corrected GAT IOP is R = 0.492 and shows moderate positive correlation and is statistically significant (P = <0.01). Pearson's Correlation Coefficient for OPA and MOPP is R =0.231, and shows a low positive correlation, and is not statistically significant (P = 0.107).

Table 2: Paired Samples Statistics for Pascal DCT and Corrected GAT

	Mean	N	Std. dev	Std. error mean
DCT IOP	15.5	50	2.08	0.2937
GAT corrected	14.6	50	3.28	0.4642

According to the paired samples t-Test, there is a statistically significant difference (P = 0.032) between the mean DCT IOP and the mean GAT IOP (corrected). This data suggests that DCT data is not interchangeable to the GAT data, and therefore one measurement cannot substitute the other.

Figure 3: XY Plot for GAT Corrected and DCT

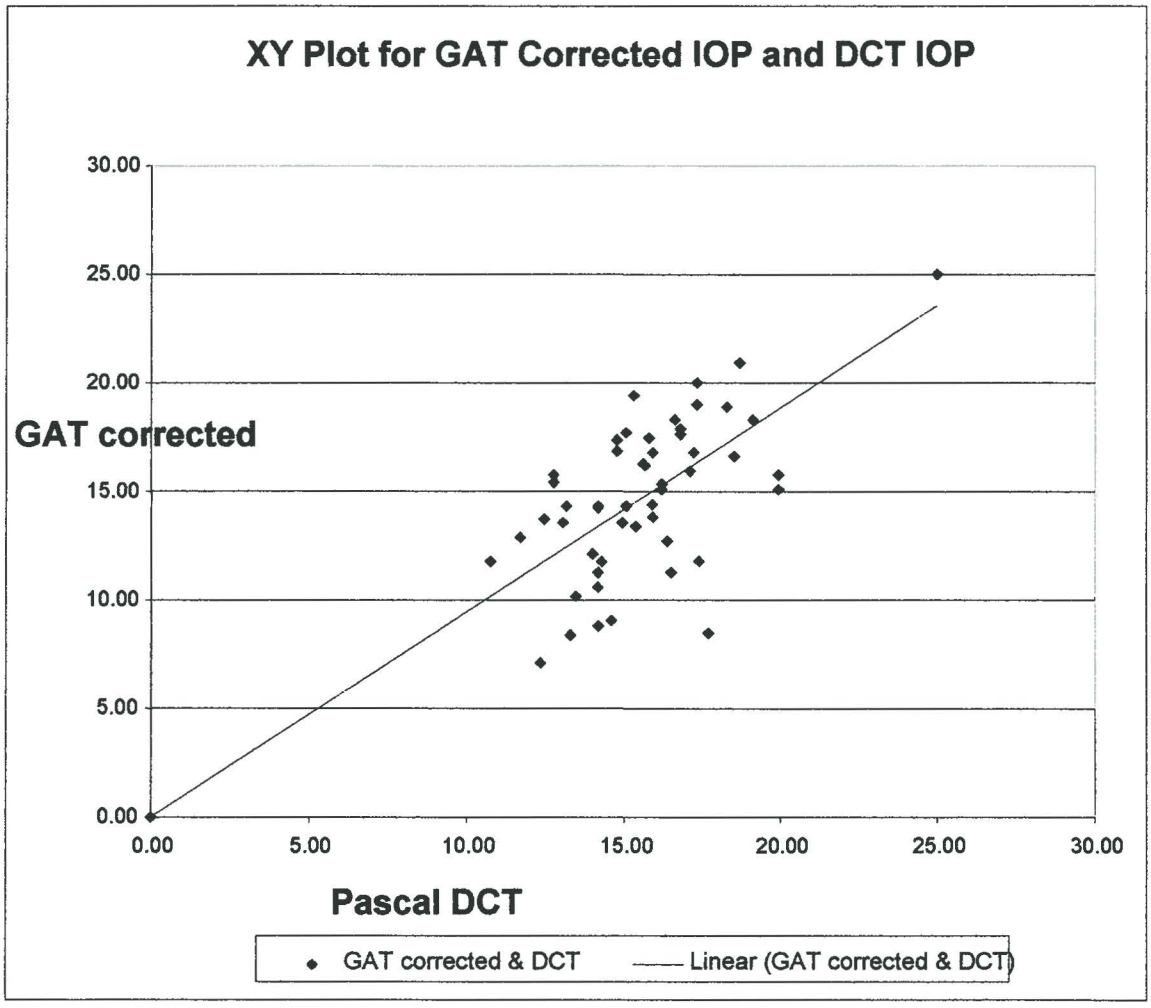


Figure 3 is the XY scatter plot for the GAT corrected for CCT and DCT. The plot shows that there is a good correlation in measurements, which is supported by the Pearson R Correlation Coefficient (R = 0.492).

Figure 4: Bland Altman XY Plot of Average IOP and Difference

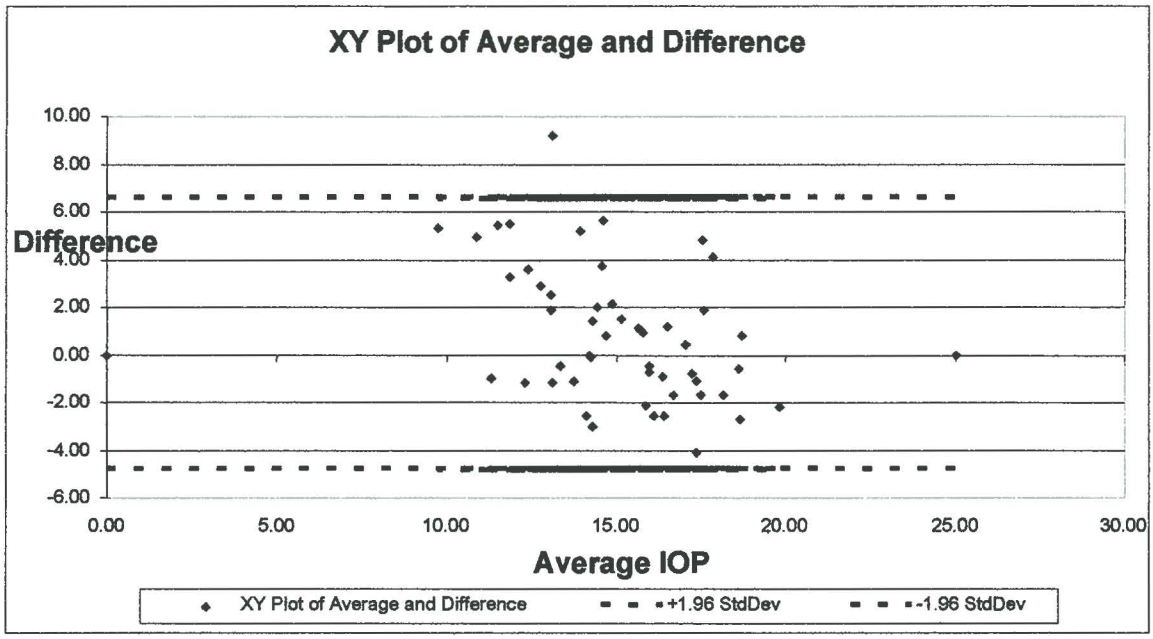


Figure 4 is the Bland-Altman XY plot of average and difference. This chart plots the average scores between the two tests against the difference between the two test scores. This chart identifies that the methods of IOP measurement are not interchangeable.

Discussion

Tonometry still is regarded as an independent risk factor for glaucoma. Although it is not the only clinical test performed in the diagnosis of glaucoma, it is still upheld as an important parameter in the management of glaucoma cases. In an attempt to uncover a more reliable method of IOP measurement for both abnormally thin/thick corneas and steep/flat corneas, many studies investigate various aspects of corneal physiology with newer methods compared to the gold standard, GAT, in both normal and glaucomatous populations.

There are several published studies comparing GAT to DCT (Kaufmann, et al. 2004, Doyle and Lachkar 2005, Kotecha, et al. 2005, Pache, et al. 2005, Ku, et

al. 2006 and Salvetal, et al. 2007). Inconsistent results in these studies are most likely due to experimental designs and offer room to conduct yet another study. Consistent with previous reports by Siganos, et al., Duba and Wirthlin, Kaufman, et al., and Kniestedt, et al., and Pepose, et al., Pascal DCT IOP measurements are higher than the GAT IOP.[20] Previous studies have found that the GAT measurement averages 1.2-2.0 mm lower than manometrically-controlled pressure measurement of the DCT.[20, 21] The value of 0.9 mm Hg in this study agrees with previously reported data of 0.94 mm Hg lower (Doyle and Lachkar 2005), 1.0 mm Hg lower (Pache, et al. 2005), 1.7 mm Hg lower (Kaufmann, et al., 2004) and 2.0 mm Hg lower (Ku, et al. 2006)[22]

Although the primary goal of this study is not to investigate corneal physiology perimeters and their effect on DCT accuracy, previous studies arrive at valid conclusions that are relevant to the purpose of assessing the clinical relevance of the DCT measurement. The Francis, et al., study, which included a normal non-glaucomatous Hispanic population, arrived at two key conclusions.[21] First, since DCT is in theory not influenced by corneal thickness, the central mean IOP should display a flatter slope when compared to GAT. Likewise, thin corneas should exhibit a lower GAT measurement when compared to DCT, and thick corneas should exhibit a higher GAT measurement when compared to DCT.[21] It was established by Francis, et al., that the measurements of DCT IOP was affected by corneal thickness but to a much less degree than that seen with GAT.[21] Second, it was discovered that DCT appears to be more affected by extremes in corneal curvature than GAT.[21, 23]

Therefore, it was concluded that although DCT may be more useful for IOP measurement in patients exhibiting extreme ranges of corneal thickness, it must be used cautiously in patients exhibiting extreme corneal curvature.[21] Johannesson, et al., supports the claim that DCT is influenced by corneal curvature.[23] These findings disagree with those of Kniestedt, et al., and Kaufmann, et al., whose research separately established that Pascal DCT is independent of corneal curvature. The statistical analysis of OPA and MOPP in this study indicates a low correlation ($P = 0.107$) and therefore cannot be considered statistically significant. The results of Punjabi, et al., discovered similar results in patients exhibiting POAG and normal tension glaucoma (NTG), citing that there was no significant association between OPA and blood pressure.[18]

Additionally while this study does not focus on the comparison between CCT and OPA, Punjabi, et al., did identify a significant negative correlation with the CCT in the glaucoma study groups. This suggested that thicker corneas caused an overestimation of diastolic IOP, thereby reducing the OPA. Likewise, thinner corneas could led to the overestimation of OPA due to underestimation of the diastolic IOP.[18] An attempt to minimize the effect of CCT on diastolic IOP was made by using the corrected value (adjusted for corneal thickness) of GAT in the calculation of MOPP. An interesting conclusion that was discovered is DCT measurements of IOP are higher than GAT in glaucoma and control subjects, but not in ocular hypertensive (OHT) subjects.[18] There is one other known method of measuring OPA: a hand-held dynamic applanation tonometer with the dimensions of a three-mirror contact lenses incorporated as an electronic pressure sensor. In addition, it simultaneously measures IOP and OPA at the

central cornea.[19] Previous studies of the SmartLens©, however, show it was not a suitable replacement for GAT.[19] In addition, Hoffman, et al., established a statistical difference in the OPA value in a normal population obtained by both the SmartLens© and Pascal DCT.[19] This most likely is due to the difference in the pressure sensor design, whereby the DCT exhibits a contour design and the SmartLens© utilizes an applanation-like tip, similar to GAT.[19]

As a pilot study, the conclusions reached from this data may offer some opportunity for further research utilizing additional clinical criteria, such as adding corneal topography and POAG and NTG patients to the subject populations. One known source of error in this study might be the Bechrakis effect, which is the intraocular pressure reduction following repeated tonometry.[24] Knowing this and the effect of applanation on central corneal thickness measurements, it is advised to allow at least two minutes of time separated between GAT and DCT measurements and five minutes of time separated between DCT and pachymetry. However, the entire data collection procedure has to be completed within 20 minutes in order to minimize the use of additional anesthetic drops, which has a known effect to make CCT thicker when more than two drops are used. The Bechrakis effect is therefore considered to minimally affect the accuracy of the data.[24]

Conclusion

Overall, the results of this study have provided additional evidence that OPA cannot be regarded an independent risk factor for glaucoma considering there is no relationship between the OPA value and MOPP in a normal population. However, it is suggested that to prove this more comprehensively, a

population study of normal versus glaucomatous populations (NTG, POAG, OHT) should be conducted. Ocular perfusion to the optic nerve head is both a prominent feature of some types of glaucoma, and a key to the development of a reliable technique of intraocular pressure measurement; therefore, these characteristics of ocular perfusion may be of value in decoding the vascular permeability theory of glaucomatous damage.

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APPENDIX A

HRSC Application Approval

FERRIS

COLLEGE OF ARTS & SCIENCES
SOCIAL SCIENCES

Connie Meinholdt, Ph.D.
Psychology Program
820 Campus Drive
Ferris State University
Big Rapids. MI 49307
(231) 591-2759

To: Dr. John Pole & Andrea Fisher

From: C. Meinholdt, HSRC Chair

Re: HSRC Applications #080503 (Title: The pascal tonometer: Ocular pulse amplitude as it relates to mean ocular perfusion pressure)

Date: June 17th, 2008

Please let me apologize for the extended review process. Personal commitments away from campus and personnel changes in the VPAA office have contributed to this delay. The Ferris State University Human Subjects Research Committee (HSRC) has reviewed your application for using human subjects in the study, "The pascal tonometer: Ocular pulse amplitude as it relates to mean ocular perfusion pressure" (#080503) and approved it under the category of *exempt – 1B*. However, please add information on how to contact the HSRC for questions or problems – Connie Meinholdt, Human Subjects Research Committee Chair, FSU, **conniemeinholdt@ferris.edu** or by telephone (231-591-2759).

Your application has been assigned a project number (#080503) which you may wish to refer to in future applications involving the same research procedure. Project approvals receive an expiration date one year from the date of approval. As such, you may collect data according to procedures in your applications until June 19th, 2009; you must apply for a renewal if data collection continues beyond this date. Finally, it is your obligation to inform the HSRC committee of any changes in your research protocol that would substantially alter the methods and procedures reviewed and approved by the HSRC in this application.

Thank you for your compliance with these guidelines and best wishes for a successful research endeavor. Please let me know if I can be of future assistance.