

Corneal Elasticity as a Measure of Intra-ocular Pressure: A Controlled Clinical Examination.

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ABSTRACT

PURPOSE: To determine the clinical efficacy of corneal elasticity (CE) measurements as an index of intra-ocular pressure(IOP). The considerable body of evidence linking elevated intra-ocular pressure (IOP) to glaucomatous conditions, points to the importance of the accurate and reliable measurement of IOP for diagnosis, prevention and post treatment assessments. Recently an applanation resonator sensor (ARS) for measuring IOP via CE has been proposed as an alternative to the extant Goldmann applanation tonometry (GAT). The present study examines the validity of the measure as an index of IOP in glaucomatous patients.

METHODS: A structured sample of glaucomatous patients and orthogonally matched normal control subjects were assessed by the GAT and ARS methods in the research and outpatient treatment laboratory of the university Ophthalmology Department. The patient sample consisted of individuals with IOP of 16mmHg and above and with evidence of clinically significant optic nerve damage.

RESULTS: Significant correlations between GAT-IOP and ARS frequency shifts (Δf_s) for both clinical ($r=.88$, $p<.001$, $n=16$) and normal subjects ($r=.60$, $p<.01$, $n=16$) were obtained.

CONCLUSIONS: The results suggest that ARS could be a clinical alternative to the extant GAT method in assessing IOP. In order to further examine the clinical efficacy of ARS- Δf_s as an accurate index of IOP, tests of a significant correlation between ARS- Δf_s and manometrically established vitreous IOP are now needed in normal and glaucomatous subjects.

INTRODUCTION

Increased intra-ocular pressure (IOP) and glaucomatous optic nerve damage (GND) have been linked in an assumed cause and effect relationship. Although it remains apparent in clinical practice that GND is most common in eyes with high IOP, the assumed unequivocal and causal status of this association has been questioned; it has also been argued that clinical attention should simply focus on the assessment of IOP levels at which the risk of GND is higher or lower than average rather than on the establishment of absolute norms of IOP.¹

With such qualifications in mind and toward that aim, measurement of IOP remains a routine investigation in eye examinations and is accepted as a fundamental parameter of ocular health and disease; it is important in the diagnosis and management of glaucomatous conditions and in the postoperative management of corneal, lenticular and vitreoretinal diseases.

The most common way to assess IOP is with Goldmann type applanation tonometry (GAT).² It has been shown to be of higher reliability and less prone to errors introduced by non-specifics than either the Tono-Pen tonometry or the Non-contact ‘air puff’ tonometry.^{3, 4}

The GAT procedure consists of adjusting the force applied by a tonometer tip on the central cornea of the patient’s eye until the observer is satisfied with the pattern produced by the visible fluorescence of the precorneal tear film. The force (in grams) is multiplied by ten and is assumed to be IOP expressed as mmHg. This procedure has over the past decades been embraced by clinicians with such a level of confidence that the errors inherent in that technique have remained largely unexamined until recently. GAT is still accepted as a standard for accurate IOP measurement although closer inspection of available data reveals sources of error that may reduce accuracy to a caliber which may be clinically significant.⁵

For example, GAT is not robust against errors introduced by corneal variants such as astigmatism, size, curvature and elasticity and epithelial abnormalities and by client variables such as age, accommodation and orientation and other non-specific diurnal or historical events and by such procedural variables as repeated measurements, placement of the probe and surgical interference, among others.^{3, 4, 6-13}

On the basis of such confounding variables most studies and reviews conclude with the caveat that GAT style assessments should be accepted with a “generous skepticism”, that there is considerable reason to believe that tonometry as commonly practiced “will not give accurate readings” and that the “unquestioned acceptance of the accuracy of GAT by ophthalmologists is still unwarranted today”.⁵ They further conclude that the Goldmann type tonometry is mostly valid in assessing IOP in individual eyes at any given time, is not efficient in comparing IOP of different individuals and should not be taken as indicating absolute IOP values. Since this method is an indirect measure of IOP occasional concurrent manometric assessments are required.

Prevailing clinical practice largely fails to adhere to these guidelines and this may primarily be due to the absence of a viable alternative. It is clear that in order to achieve a more accurate diagnosis of clients at high risk levels of GND, and establish prophylactic protocols and post treatment assessments, there is now a pressing need for an IOP assessment instrument which is simple, more reliable and robust against the above sources of errors.

Toward that end a new sensor for IOP measurement has recently been proposed.^{13, 14} Their applanation resonator sensor (ARS) is based on a piezo-electric element that is set to vibrate with its resonance frequency and when attached to soft tissue will produce a resonance frequency shift (Δf_s) which can be used to gauge the softness or elasticity of such tissue (for details see also *Apparatus*). The resonator was designed by Bioresonator AB of Sweden and was originally intended to test the elasticity of skin and muscle tissue. Eklund *et al.* evaluated its suitability to measure the elasticity of the cornea and its relationship to IOP with a silicon and an *in vitro* pig eye model and subsequently with *in vivo* human eyes of healthy volunteers. The authors report a low but significant correlation between GAT-IOP and ARS- Δf_s and suggest that this new method should be further tested and refined with a view to its clinical utility as an index of IOP.

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In order to make meaningful comparisons between the two methods GAT-IOP would have to be accepted as the best available standard definition of IOP; that is, notwithstanding the above cited sources of error and cautions regarding its limited validity as an absolute measure, it can be considered a reliable and valid measure of IOP against which other approaches could be gauged.¹⁵

Such a fresh series of examinations should ideally consist of cross-sectional and longitudinal clinical tests with the substantive and procedural attributes which allow a further judgment of the nature of the GAT-IOP - ARS- Δ fs relationship and its clinical utility. For example, ARS- Δ fs should be compared with manometric and GAT measures in clinical GND patients and normal volunteers orthogonally matched with respect to sources of error above (e.g., corneal, subject, historical and instrument variables). If a significant and clinically meaningful correlation between the two can be established, the ARS- Δ fs procedure should be further evaluated in a clinically controlled manner with respect to its robustness against such errors and confounds as compared to GAT procedures. In addition, longitudinal examinations could be of value in testing the clinical predictive power of ARS- Δ fs measures with respect to subsequent GND in the high risk population. This evokes technical and ethical issues which remain to be addressed.

Such a battery of tests is clearly beyond the scope of a single effort. The present study is thus a simple first step toward the development and evaluation of the ARS- Δ fs procedure and its clinical application. For this purpose a clinical GND group and matched group of normal volunteers are compared with respect to ARS- Δ fs and GAT-IOP measurements. It is hypothesized that the two groups differ significantly in terms of the two measurements and that a significant negative correlation exists between the two measures for both groups.

METHOD

Subject Characteristics

Subjects were all volunteers from the Miyazaki Medical College, Department of Ophthalmology. They were told that the test was part of a survey but not informed of the hypotheses involved. *

The clinical group consisted of individuals who were referred to the Department of Ophthalmology with a GAT-IOP at or above 20 mmHg, showed evidence of optic nerve damage, were free of any retinal deterioration, had no other related illnesses and had not received either chemical or surgical treatment of any kind. These requirements served to control for possible confounds related to such variables.

The control group consisted of individuals recruited from hospital staff members with GAT-IOP of 17 mmHg or less, who had no illness of the eye, had normal or corrected vision and showed no record of other problems requiring medication or other interventions.

* The instructions and procedures were examined by and found to conform to the requirements of the ethics committee of the institution.

Since there is as yet no clear evidence that gender influences IOP assessments, and since there is some evidence that age does³ the two groups were

matched for gender and orthogonally matched for age. The orthogonal nature of the latter is essential; most clinical studies report the group age as means or other measures of central tendency; this ignores extreme scores and renders a false assumption that groups are controlled for age.

Subject Recruitment

It was not possible to collect a sufficient number of clinical subjects with the above attributes who had not yet received any kind of treatment and then commence the planned assessments. The time required for such an effort would relegate high risk GND patients to a waiting list involving several months of delay in the treatment until the full sample is collected and this would obviously create an ethical problem.

The recruitment was therefore restrained to a first-come-first-served method. A patient referred for elevated IOP was initially assessed with GAT and retinal photographs were examined by both the experimenter and subsequently by a blind colleague to confirm the presence of GND and the absence of retinal disease. If the subject's condition and attributes conformed to all the above requirements the planned tests were performed as described below. Concurrently, normal control subjects, matched for age + or -- 3 years and for gender, were yoked to clients. In this manner 25 clinical and 25 control subjects were recruited over a period of 11 months.

Of these 6 clinical subjects were eliminated during the testing phase of the study due to repeated faulty contact of the ARS probe with the cornea; the reason for this is as yet unclear. The control subjects associated with this fault were also removed. This left a final sample of 16 subjects in each group consisting of 10 females and 22 males with an age range from 24 to 68 years (see also *Table 2*, Results,).

Apparatus

A Goldmann applanation tonometer and applanation resonance sensor were used. The same Goldmann applanation tonometer, Inami Company, Japan, model L-5110A91 was used throughout the study and calibrated before each assessment with a kit according to the manufacturer's recommendation.* The device, its rationale and use have been repeatedly described in detail elsewhere^{5, 16} and suffice it here to say that it consists of an optical head with a special prism mounted on a force balance which, in turn is mounted on a biomicroscope. The flat contact surface of the optical head is pressed against the cornea and the operator adjusts the contact force with the force balance until a predefined contact area is obtained; IOP can be deduced from the contact force in grams converted to mmHg.

The reliability of this instrument was further tested by subjecting four healthy volunteers to repeated measures over nine test occasions with a five second inter-trial interval. A visual inspection of the resulting descriptive statistics in *Table 1* suggests that the apparatus yielded measures of a within subjects consistency sufficient for this study.

GAT-IOPmmHg									
Test Occasions									
Subjects	I	II	III	IV	V	VI	VII	VIII	IX
①	9	10	9	9	10	10	9	10	10
②	18	17	17	18	17	17	18	17	17
③	20	19	18	18	18	18	20	19	18
④	16	16	16	16	16	17	16	16	16
Total	63	62	60	61	61	62	63	62	61
Average	15.75	15.5	15	15.25	15.25	15.5	15.75	15.5	15.25

Table 1. Goldmann applanation tonometer (GAT) intraocular pressure (IOP) measures (mmHg) of four normal subjects over nine test occasions.

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Grand totals, averages and standard deviations

	Total	Average	S. D
①	86	9.55	0.527
②	156	17.33	0.5
③	168	18.66	0.866
④	145	16.11	0.333
Grand	555	Grand 15.41	Grand 0.557

ARS- Δ fs of the cornea was determined with an applanation resonator sensor. The same device used throughout the study was a *Venustro System* model *Venustron II* with a *Venus Data Convert* computer program distributed by Axiom Co., Japan.* This model is equipped with a self-calibrating capacity and was interfaced with a computer which permitted the automatic recording of data in digital form. The oscillator and the basic principle underlying its function and operation have been described in detail earlier.^{17, 18} In brief, its main components are a piezo-electric element made of lead zirconate titanate, a contact piece and a feedback circuit that drives the element and sustains the oscillations in the response frequency of the system. When the rod shaped sensor is brought into contact with the cornea (loaded condition), a new oscillation system is formed with a new resonance frequency. The output from the system is a change in frequency between the unloaded and loaded conditions expressed in Hz as Δ fs. Although Eklund *et al.*¹³ are examining the utility of a spherical probe, the manufacturer's rod shape probe was used in the present study.

Procedure

In order to better compare some of the results with the examination of 25 normal subjects by Eklund *et al.*¹³ an attempt was made here to match theirs. However, this was only partially successful. The procedures differ on two aspects. First, since the present study included a clinical group with a problem of high risk of GND, the test had to be conducted upon admission rather than from a complete sample drawn at random from a clinical

*The authors do not have any commercial or proprietary interest in these devices or the company producing them, nor do they have any financial interest or receive payment as a consultants, reviewers, or evaluators.

population. Second, the number of measurements per eye was limited to three, rather than six, in order to better control for any possible testing effect.^{5, 19, 20}

With subjects in the traditional seated position and after local anesthesia and fluorescein instillation in both eyes, IOP or Δ fs was measured three times in each eye with GAT or ARS respectively. Following a 10 minute pause, the procedure was repeated with the other method; the sequential order between the two methods was randomized. The total time to take the three measures was about 1 minute. The same examiner performed tonometry. The mean of three readings for each eye pooled was used for calculations.

Statistics

The non-parametric *Mann-Whitney U Test* was used to compare GAT-IOP and ARS- Δ fs means for the two groups. Although this test is less powerful and more conservative than

parametric tests, the assumptions underlying the latter could not be met; i.e., sufficient *n*, normal distribution of the sample and cardinal scale data.

The Pearson's rank order coefficient was used for correlation analysis and $P < 0.05$ was considered statistically significant.

RESULTS

Table 2 shows the GAT-IOP (mmHg) and ARS- Δ fs (Hz) data used for analysis of every subject in the clinical and control groups; each of the data points is an average of six measurements, that is, three measurements of each eye pooled for both methods.

Glaucoma Patients				Normal Control Subjects			
Subjects	Age/Sex	GAT-IOP mmHg	ARS- Δ fs Hz		Age/Sex	GAT-IOP mmHg	ARS- Δ fs Hz
1	60M	25	239		61M	12	496
2	57F	53	36		57M	9	564
3	63M	34	141		61F	14	411
4	64M	35	260		63F	12	199
5	66M	34	131		64M	17	185
6	67M	34	139		67M	15	218
7	71M	45	80		70M	12	178
8	31F	46	122		28F	16	204
9	57F	53	57		57M	7	503
10	66M	55	90		64M	10	376
11	68M	28	202		65M	17	258
12	66M	20	310		66F	17	165
13	74F	21	303		77M	12	178
14	24F	22	280		25F	16	204
15	71M	25	239		70M	12	193
16	67M	30	128		67M	17	335
Total		560	2575			215	4667
Ave.	60.7	35	172.3		59.9	13.4	291.6
S.D		11.93	89.6			3.16	135.9

Table 2. Intraocular pressure (GAT-IOP) and applanation sensor frequency shift (ARS- Δ fs) in Glaucoma patients and normal control subjects.

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A comparison of the GAT-IOP group averages shows a higher mmHg reading for the clinical group; this is not surprising since subjects were selected on that basis. This difference proved statistically significant (*Mann-Whitney U*, $n=16$, $p<0.001$). Conversely, the comparison of the ARS- Δf_s averages between the groups showed a higher reading for the normal control group. This difference proved also statistically significant ($p<0.0158$). *Figure 1* depicts this inverse relationship between the two measures.

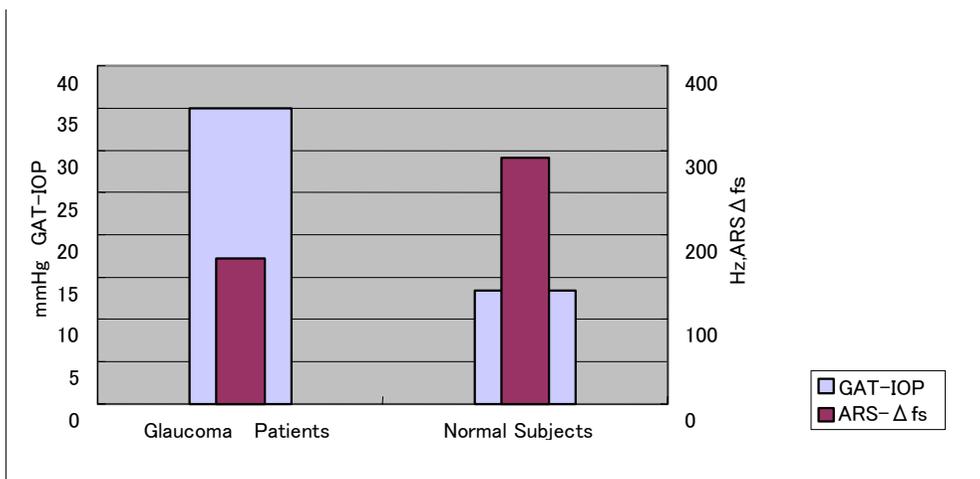


Figure 2 shows GAT-IOP plotted against ARS- Δf_s for normal control subjects indicating a negative correlation. This association proved significant (*Pearson* rank order coefficient $r=-0.60$, $p<0.015$, $n=16$). *Figure 3* shows the same plotting for the clinical group; the negative association between the measures also proved significant ($r=-0.88$, $p<0.001$, $n=16$).

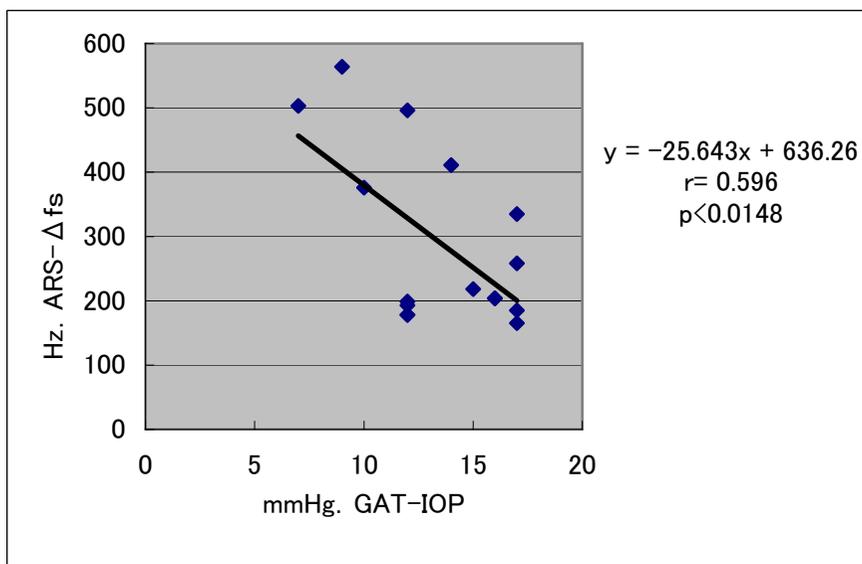


Figure 2 Correlation between intraocular pressure (GAT-IOP) and applanation sensor frequency shift (A Figure 2RS- Δf_s) in normal control subjects.

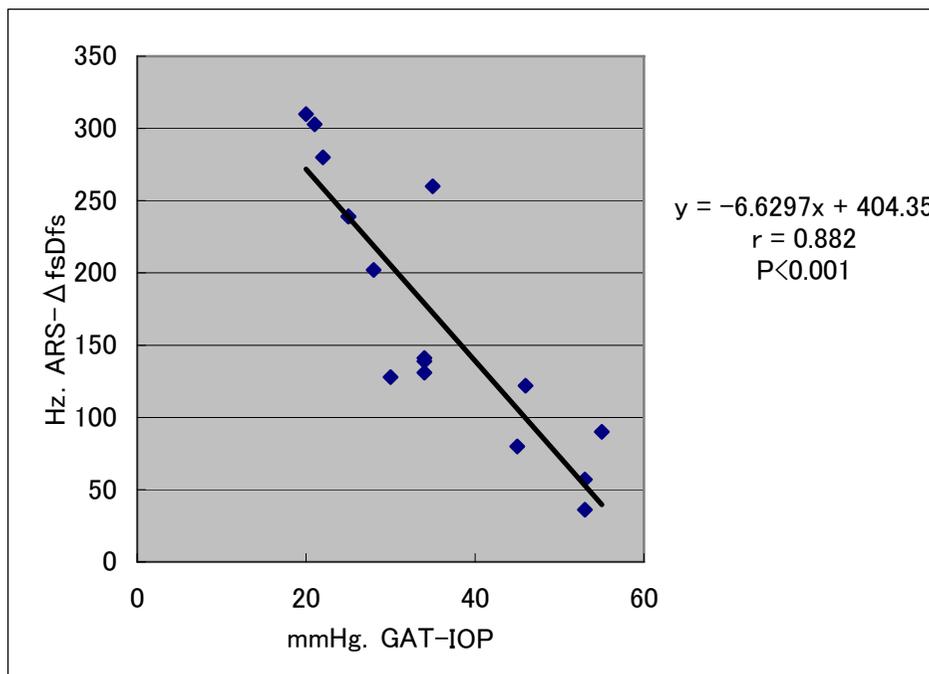


Figure 3 Correlation between intraocular pressure (GAT-IOP) and applanation sensor frequency shift (ARS-Δfs) in Glaucoma patients

In summary, the significantly higher GAT-IOP of the clinical group indicates that the clinical intake criterion for that group was successfully met and the significantly higher ARS-Δfs in the same group conformed to the earlier prediction to that effect. So did the significant negative correlations between the two measures in both groups, that is, greater ARS-Δfs shifts were associated with lower GAT-IOP; however, the correlation was stronger in the clinical group. The size of effect or variance accounted was calculated as 36% for the control group and 77% for the clinical group.

DISCUSSION

Hypotheses and replications

In this study the association between intraocular pressure (IOP) and frequency vibration shift of the cornea (Δfs) was examined in patients with glaucomatous optic nerve damage (GND) and elevated IOP, as measured by the traditional Goldmann tonometry (GAT) and in normal volunteers, in order to further test the efficacy of the applanation resonator sensor

(ARS) as a diagnostic tool. The results show that the observed Δfs values of the ARS device significantly discriminate between subjects of normal and elevated GAT-IOP and that such measures significantly correlate with measures of GAT-IOP. The hypotheses that the clinical and control groups significantly differ on both measures and that a negative correlation exists between GAT-IOP and Δfs were thus confirmed.

The results also partially confirm those of Eklund *et al.*,¹³ who reported a weak but significant negative correlation between the two measures in normal volunteers - only to the

extent that the correlation in our normal subjects was also weaker when compared to that in the clinical group. It may well be that the ARS- Δf_s method better discriminates among elevated IOP levels; however, Eklund *et al.* did not include a clinical group in their study and this aspect of the present study needs to be confirmed by replication elsewhere with studies of different designs.

Such attempts to test a possible link between Δf_s and IOP in clinical samples need to attend more stringently to concerns of the external and internal validity and reliability with respect to the procedural and substantive issues in experimental protocols.

External validity and indirect measures of intraocular pressure

If external validity concerns the extent to which a device or method actually measures what it purports to measure, in the present study the ARS device cannot be said to measure IOP directly; rather it measures the corneal elasticity (CE) and, similar to Goldmann's measurement of mmHg resistance to applanation, constitutes a *correlate* of true IOP. It was thus speculated in the present study that the level of CE might be related to IOP in that more elastic corneas might be associated with normal or lower IOP and conversely that a decrease in the elasticity of the cornea might be associated with clinically elevated IOP.

However, here, as in other studies of this kind, CE values were correlated with another correlate of IOP, i.e., GAT-IOP, and not with IOP *per se*. The crucial issue of external validation thus remains; that is, to what extent CE (ARS- Δf_s , Hz) correlates with true manometrically assessed vitreous pressure in the *in vivo* human eye. In the absence of such basic validation attempts we may eventually be in danger of eating the menu instead of the dinner by producing correlates of correlates at the cost of accurately assessing the clinical utility of indirect measures such as the one proposed here. This is not to say that such correlates among indirect measures are not of significance; what we are saying is that by themselves they are not sufficient to establish the external validity of CE measures as an index of IOP.

As Witacre and Stein point out,

*“If accurate IOP assessment is required to make an important clinical decision...then consideration should be given to performing simultaneous manometry and tonometry... although clinicians are presently reluctant to perform manometry in living eyes...”*⁵

Such conclusions not only suggest that GAT-IOP and similar correlates of IOP are not sufficiently validated, but also indicate that direct manometric assessment of IOP is still difficult and inconvenient in the routine clinical examinations; it is time consuming, relatively complex and involves considerable patient discomfort. However, whereas such constraints may be valid arguments in clinical practice, they cannot be defended in clinical-experimental investigations, because of their far reaching consequences for clinical practice.

In order to establish the external validity of the newly proposed CE as an index of IOP, it should be subject to rigorous comparisons with manometric measures of IOP. This requires also renewed attention to issues of the internal validity and reliability of clinical-experimental designs.

Internal validity and reliability in clinical studies of intraocular pressure

If the internal validity concerns the extent to which variables within a clinical-experimental examination are operationalized and controlled to prevent confounds and

reduce the interference of non-specifics, the present study shows assets and liabilities common to most clinical-experimental paradigms.

The present results can be accepted with a high degree of internal validity in that the clinical group was rigorously controlled in terms of the definition of glaucomatous symptoms, ongoing therapy, age and gender and was orthogonally matched with the normal control group and in that tests were conducted with a high level of procedural constancy.

However, there were also some, albeit few, design and procedural aspects which could potentially compromise both the validity and reliability of the results to some degree, aspects which should be prevented in future examinations of this nature. Paramount among these are the potential for experimenter error and bias, instrument decay and other historical confounds and the relative low number of subjects.

The possibility of experimenter bias rests in the way IOP measures were obtained. Although the ARS device was automated in that Δ fs readings were automatically entered into a computer program independent of the examiner, to the knowledge of the author the Goldmann applanation tonometer has as yet no such automated feature; the examiner adjusts the device manually, reads the result and then manually enters it into some form of storage, e.g., a written record or a computer via the keyboard. This procedure is clearly open to the myriad of unwitting experimenter errors or biases which have been reported for the past decades as the *Rosenthal Effect*. Whereas in clinical assessments such errors may be of lesser significance, in experimental examinations where an attempt is made to create more sensitive and accurate instruments, experimenter effects have a high probability of becoming a significant confound. If the relationship of two measures in one subject is examined, such potentials for error should be held constant or should be controlled in both procedures of measurement. Thus in the present study automated and blind recording of data for both assessment modes would have enhanced the internal validity considerably and it should be an essential feature in subsequent replications.

The potential for a confound of instrument decay and historical factors was introduced by the necessity of assessing subjects with the same instruments over a period of twelve months. As will be recalled, this had to be so for ethical reasons in that it would not be acceptable practice to relegate high risk GND patients to a waiting list until a sample group has been established for as long as one year later; thus measurements had to be completed as patients reported.

This required also the frequent calibration of instruments. Although the ARS probe has a built-in automated self-calibration feature which can be consulted after each measurement, at present and to the best knowledge of the authors, the Goldmann type tonometer has no such features and needs to be calibrated by hand with a kit provided by the manufacturer; here again the experimenter effect looms large and an automated procedure for both measuring devices is desirable. In addition, the continued use of such an instrument over a long period of time may introduce other as yet undetected decay factors (e.g., optical and mechanical deterioration, etc.). Such shortcomings may compromise the reliability of the tonometer and remedial attempts are required in order to ensure its constancy.

Similarly, the relatively long period of twelve months required to complete all measurements leaves the experimental process open to a variety of historical confounds which may not be desirable. Such problems can be controlled by obtaining a sufficiently large existing client population to allow sampling and assessments to be completed in a relatively brief time (i.e., days rather than months). However, the stringent attributes required of a group like our clinical group makes the timely accumulation of such samples difficult.

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The low number of subjects examined in the present effort (16 clinical and 16 control subjects) is relevant to both external and internal validity. This limitation is again the result of a trade off between the stringency of subject attributes demanded and the availability of such subjects in the clinical population. The low number required an analysis with non-parametric statistics which may lead to the underestimate of significance levels. Again, the access to representative samples from a relevant clinical population of sufficient size is crucial.

Finally, there is a need to test the ARS probe for its robustness against the sources of error inherent in GAT. Among these, irregularities of the cornea, area of probe contact and placement on the cornea loom large.

The recent attempts by Eklund *et al.*¹³ to modify the ARS probe in order to reduce its sensitivity to such confounds and thus enhance its validity and reliability are a promising beginning.

CONCLUSION

In this study it was found that the corneal elasticity as measured by ARS- Δ fs correlated negatively and significantly with intraocular pressure defined as GAT-IOP in clinical GND patients and matched normal controls. This was interpreted to mean that corneal elasticity is inversely related to IOP and that ARS- Δ fs measures may therefore be a reliable index of IOP and thus of significant clinical utility. However, ARS- Δ fs and GAT-IOP are assumed correlates of true IOP and in order to further test ARS- Δ fs for clinical use there is now a need for examinations which primarily test the relationship of ARS- Δ fs measures with the true manometrically assessed vitreous IOP. Several critical issues of validity and reliability hitherto ignored in such efforts have been identified and need to be addressed in future examinations of this device. These include refinements in instrumentation and procedure of assessment, availability of sufficiently large representative samples from appropriate clinical populations and the control of non-specific confounding subject variables by orthogonal matching of clinical and control groups. It was suggested that this new method might be a promising alternative to the extant Goldmann type tonometry.

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