Role of IOP in the definition, diagnosis and management of glaucoma has been on a roller coaster. Till few years back glaucoma was synonymous with intraocular pressure (IOP). If the IOP was more than 22 mm Hg, IOP lowering agents were started; this is still practiced by quite a few ophthalmologists. IOP was one of the most important component in the definition of glaucoma. However, with the knowledge that we gathered from various population-based studies we realized that very high number of patients with glaucoma (at least 50% in various population based studies) shows IOP < 21 mm Hg. Also, the information about the natural history of glaucoma has revealed that despite lowering IOP to early teens, glaucomatous optic neuropathy continues to progress in few patients. This article is an attempt to define the concept of target IOP and how its identification can be of relevance to the glaucoma practitioner.

WHAT IS IOP?

It is the pressure inside the eye to maintain the integrity of the globe. Maintenance of IOP is a faculty of aqueous humor, which is continuously secreted from the ciliary epithelium of ciliary processes. IOP in an eye is dependent on two factors: (a) rate of aqueous humor formation (b) facility of aqueous outflow. The increasing knowledge about this led us to realize the limitation of IOP as a main criterion for diagnosis of glaucoma. In 1996, American Academy of Ophthalmology’s preferred practice pattern for primary open angle glaucoma recognized that IOP is neither a component of definition of glaucoma nor a clinical characteristic of it. Presently, IOP is considered as one of the causal risk factor for glaucoma and its progression. However, the fact remains that at present in the armamentarium of glaucoma management, treatment of IOP is the only available treatable option that reduces RGC loss.

For simplicity and better understanding, we would describe the present article under the following headings:

1. What is IOP?
2. Techniques of IOP measurement and related errors.
3. Role of IOP in glaucoma diagnosis.
4. Role of IOP in glaucoma management and Target IOP.
5. Role of IOP in glaucoma screening.
6. Myths generated by inappropriate interpretation of recent RCT’s (Randomized controlled trials) in relation to IOP.
7. Do’s and Don’ts in raised IOP.
South Indian population (Vellore and Andhra Pradesh Eye Disease study) also reported mean IOP of 15.5 mm Hg (2 SD: 9-22.6 mm Hg). Normal distribution of IOP in a population is not Gaussian but is skewed towards right. This skewness indicates that in a population, individuals with IOP > 21 mm Hg should be more than 2.5%. One can draw inference from this that there is no upper cut-off for normal IOP and that 5% of the normal individuals would have IOP above or below this range.

TECHNIQUES OF IOP MEASUREMENT

Since the invention of applanation tonometers in early 1950’s, till date, Goldmann applanation tonometer (GAT) is considered the gold standard for IOP measurement. Reported inter- and intraobserver variability of GAT is up to 2 mm Hg.

Some of the important factors affecting the measurement of IOP with GAT are:

1. **Corneal astigmatism**: GAT underestimates 1 mm Hg for every 4 Diopter of with-the-rule astigmatism and overestimates 1 mm Hg for every 4 diopter of against-the-rule astigmatism. Goldmann method or Holladay method can be used for accurate IOP measurement.

2. **State of corneal hydration**: GAT underestimates IOP in corneal edema. However, in mild corneal edema secondary to contact lens, the GAT may overestimate IOP.

3. **Central corneal thickness**: GAT underestimates IOP in thin cornea and overestimates in thick cornea.

We would briefly describe the various newer tonometers available today in the market.

**Ocular Response Analyzer (ORA)**

Corneal hysteresis, a measure of corneal viscoelasticity, can affect IOP measurement. Currently, Ocular response Analyzer (Reichert, Inc., Depew, NY) has a property to measure corneal hysteresis. It calculates corneal hysteresis (indicated on the ocular response analyzer as CH), the corneal resistance factor (indicated as CRF), the Goldmann-correlated IOP (indicated as IOPg), and a “corneal compensated” IOP (indicated as IOPcc) (Fig. 1).

**Dynamic Contour Tonometer**

The Pascal Dynamic Contour Tonometer (Pascal DCT; Zeimer Ophthalmic Systems AG, Port, Switzerland) works on the principle of contour matching to measure IOP as well as ocular pulse amplitude (Fig. 2). This device is based on Pascal’s Law of Pressure. The concave shape of the tip generates minimal corneal distortion and theoretically eliminates errors in measuring IOP induced by ocular rigidity when the cornea is applanated with a flat-tipped tonometer.

In a recent, prospective, in vivo clinical study, IOP measured by the Pascal DCT was within 1 mm Hg of the intracameral pressure measured manometrically with a reference pressure sensor over a wide range of pressures. DCT consistently measures 2 mm Hg high IOP compared to GAT.

**Rebound/Impact Tonometer (RBT)**

It is based on bringing a magnetized probe into contact with eye and detecting its return bounce motion with a sensing coil. Good correlation is observed between GAT
and RBT ($r = 0.9$), but RBT readings are consistently higher than GAT (median: $1.8 \pm 2.8$ mm).

Pressure phosphene tonometer: It is a self-tonometer based on the principle of entoptic phenomena of pressure phosphene. It is measured over eyelid.

It’s reproducibility is good in patients whose IOP are less than 25 mm Hg.

NCT (Noncontact tonometer) is based on the principle of corneal applanation but uses a puff of air to flatten (applanate) the cornea and hence is liable for the same limitation as GAT. An additional source of error in NCT measurements is that IOP is determined at a single very brief instant in time and IOP can pulsate considerably over time as the choroid fills with blood and then empties in concert with the cardiac cycle. (To some degree, Goldmann takes this pressure variation into account because measurements are made, when the inner aspects of the pulsating mires just touch).

Errors Related to IOP Measurement

1. **Errors:** There can be intraobserver measurement error which may account up to 2 mm Hg, and the inter observer variation in IOP measurement is approximately 3 mm Hg. If GAT is not calibrated at regular interval (at least once in 6 months), the reading can be fallacious.

2. **Regression to the mean:** All biological parameters (IOP, blood pressure, etc) have tendency to regress toward mean value when measurement is rechecked. So, if first measurement records 22 mm Hg, then the chances of recording IOP less than 22 mm Hg in next session is higher.

3. **Central corneal thickness (CCT):** As GAT is still “Gold standard” for IOP measurement, we need to discuss this one of the important limitation of GAT briefly. GAT overestimates IOP in thick cornea and underestimates IOP in thinner corneas. Use of nomograms to convert this IOP to “true IOP” is not accurate. There are various other factors, which also influences IOP measurement (like corneal rigidity) that compounds this issue. From research point of view, using Ehler’s formula makes sense, as it is more rigid. However, there is no consensus as to which formula is correct. We encourage people to classify their patients into three groups: thin cornea, normal cornea and thick cornea.

### Role of IOP in Glaucoma Diagnosis

Initially, raised IOP was considered synonymous with the optic nerve damage and hence glaucoma. Now, it is well known that IOP is only one of the causal risk factor for glaucoma. In EMGT study, nearly 50% of the patients were diagnosed as normal tension glaucoma (NTG) at the time of presentation. In Baltimore eye survey, 50% of the patients had IOP below 21 mm Hg at the time of first presentation. This result poses a problem as to what level of IOP is safe for the patient or in other words when to say that patient does not have glaucoma. There is sufficient evidence available to second the fact that higher the IOP, more is the risk of developing glaucomatous optic neuropathy. Also, in patients with asymmetric IOP, disk and field damage are more in eyes with high IOP. The blue mountain study found the odds ratio of developing glaucoma was 4.7 times higher in patients with a screening IOP of greater than 21 mm Hg than in patients with IOP $< 21$ mm Hg. Sommer et al found that as the baseline IOP increases, percentage of eyes having field damage increases along with the relative risk (Table 1).

With OHTS and EMGT studies, the cause and effect relationship has become clearer. In EMGT, in treatment group 45% showed progression as opposed to 62% in control arm. In OHTS 10% progressed in control arm opposed to 4.5% in treatment group. It was also shown in OHTS that as baseline IOP increases (at normal range of CCT), the risk of conversion to glaucoma increases. Both studies clearly show contributory effect of IOP on glaucoma causation and progression.

<table>
<thead>
<tr>
<th>Baseline IOP (mm Hg)</th>
<th>% Developing field loss</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;16</td>
<td>0.8</td>
<td>1</td>
</tr>
<tr>
<td>16-19</td>
<td>1.4</td>
<td>1.7</td>
</tr>
<tr>
<td>20-23</td>
<td>3.1</td>
<td>4.0</td>
</tr>
<tr>
<td>&gt;24</td>
<td>8.4</td>
<td>10.5</td>
</tr>
<tr>
<td>&gt;30</td>
<td>41.2</td>
<td>15.3</td>
</tr>
</tbody>
</table>

It must be emphasized that as IOP is a dynamic variable; single IOP reading just like blood pressure reading has little significance in diagnosis and one should not rely on one single reading. Diurnal variation in IOP (up to 5 mm Hg), interobserver and intraobserver variability (up to 2 mm Hg) should be considered normal. However, a single IOP reading
of > 30 mm Hg (rechecked one more time) is sufficient enough to consider treatment after correlating for other ocular factors. If the IOP is in low teens or early twenties, multiple readings of IOP measured at regular intervals on a single day or over a period of few days at different hours of the day, known as Diurnal variation test (DVT), can aid in the diagnosis of glaucoma. Diurnal IOP fluctuation of 8 mm Hg or more on DVT is an independent risk factor for glaucoma progression. DVT also helps to differentiate Normal tension glaucoma (NTG) from POAG and 24 hours control of medical management.

**Role of IOP in Glaucoma Management**

From the management standpoint the glaucoma specialists have gone through the stage of being insecure that there is no evidence for the way they are treating their glaucoma patients by lowering the IOP. The recent clinical trials once again have bolstered our confidence in glaucoma management by lowering the IOP.

**Rationale Behind IOP Reduction**

Primary aim in the overall management of glaucoma is to prevent the loss of retinal ganglion cell (RGC) loss. Normal age related yearly decay of RGC’s is approximately 5000–7000 cell loss per year. Over and above these age related loss, retinal ganglion cells are also susceptible to other external factors those may be pressure dependent or pressure independent. There has been increasing evidence from the clinical trials that the reduction of IOP leads to visual protection (indirect evidence of RGC protection). AGIS reported that the risk of progression is least in patients with IOP constantly below 12 mm Hg. EMGT showed that glaucoma progression slows down, if the IOP is reduced by 25%. However, still we are not able to define the lower limit of acceptable IOP as well the upper limit to limit the RGC loss. Many glaucoma patients, including both open-angle and angle-closure subtypes, tolerate remarkable elevations of IOP for long periods of time without demonstrable damage. With this perception came the concept of target IOP.

**What is Target IOP?**

Target IOP can be defined as the highest IOP in a given eye at which no clinically apparent nerve damage occurs OR it can be also defined as the IOP at which the sum of the HRQOL (Health-related quality-of-life) from preserved vision and the HRQOL from not having side effects from treatment is maximized.\(^5,^7\)

Target IOP is not a fixed or a magical digit but it is a customized range based on patient’s clinical profile and glaucomatologist’s experienced guess. It’s a range below that RGC loss can be maximally minimized or above which RGC loss or chances of patient going blind would be minimized.

The following factors should be considered to individualize the target IOP:

- The functional damage on WWP
- Structural damage: optic disk and retinal nerve fiber layer (RNFL).
- Baseline IOP at which the damage occurred
- Age of patient
- Presence of additional risk factors

There are various tables and formula to calculate target IOP.\(^8\)–\(^11\) Target IOP calculation has to be individualized based on patient’s clinical profile. While we can formally calculate this, the rule of thumb is: go on to reduce at least 20% in mild, 30% in moderate glaucoma and more than 40% in severe glaucoma.\(^10\) The higher the IOP, the more profound percentage reduction will be required.

Below, as an example, we have provided Jample’s formula for calculating target IOP.

\[
\text{Target pressure} = \left[ \text{IOP} \times \frac{1}{100} - Z + Y \right] \pm 1
\]

\[
Z = \text{Optic nerve damage}
\]

0. Norm disk Norm Field
1. Abnormal Disk Norm Field
2. Field loss not threatening fixation
3. Field loss threatening fixation

\[
Y = \text{Burden of therapy}
\]

No effects on QOL
Small effect
Moderate effect
Large effect

In an advanced glaucoma in a young or middle-aged patient, as evident by structural and functional damage, one may choose to reduce IOP by 50% from the baseline. However, in a very old patient, if a same clinical setup demands more number of medications, one may set target IOP to a slightly higher level. This will improve his quality-of-life for the rest of his expected life. In other example of
mild to moderate structural or functional loss, if the presenting IOP is in early twenties, you may aim for 20% to 25% IOP reduction from baseline. However, the presenting IOP of 50 mm Hg or more may call for greater IOP reduction.

However, there are limitations of target IOP approach. Optimal target IOP may be different for different individuals depending on the severity of the disease and there is no sure shot method to know the true target IOP of an individual. It is an educated guess. The information gained from the tests performed on patient, the rate of visual field progression and other factors in the patient’s history assist in estimating and modifying target IOP. This range of target IOP should be modified if necessary rather than adhered to strictly.

Role of IOP in Glaucoma Screening

Screening for disease in a population has always been an emotional issue and in principle it makes sense to pick up disease in early stage and treat them, so we can reduce irreversible blindness as far as glaucoma is concerned.

The World Health Organization recommends that certain defined criteria be fulfilled before any population based screening is undertaken for any disease. Few of these criteria does fit for glaucoma. For screening we need a test with high positive predictive value (so as to reduce more normals requiring referrals to rule out the “disease” they are labeled with). The predictive value of a test is dependant on the prevalence of glaucoma in the population being tested. As shown in the Figure 3, assuming all other factors remain constant, the positive predictive value (PPV) increases with increasing prevalence.

With a low prevalence of glaucoma, most of those who are test positive will in fact be false positives.

As far as IOP is concerned, applanation tonometry, has poor sensitivity and moderate specificity for the detection of glaucoma. For the detection of POAG, at a cut off of > 21 mm Hg, applanation tonometry has a sensitivity of 47.1% and specificity of 92.4%. Half of all patients with POAG have IOPs below 22 mm Hg at a single screening. Further, many individuals with raised IOPs may never develop optic nerve damage. IOP measurement alone is an inefficient tool to screen populations for glaucoma. If we use population based data for glaucoma (2% prevalence of glaucoma with IOP > 21 mm Hg) and calculate PPV using 2X2 table (Table 2), we can see that one in nine patient we send for confirmation will have glaucoma and eight of nine would be false positive. On other hand negative predictive value is 99%, which means we are 99% sure that this patient does not have glaucoma. This figure looks fantastic but when we started screening in a population (with a prevalence of 2%) we were already 98% sure that our patient does not have glaucoma (even before we checked IOP).

Table 2: Positive predictive value of IOP for population based screening

<table>
<thead>
<tr>
<th>Test</th>
<th>Positive</th>
<th>Negative</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>94</td>
<td>784</td>
<td>0.11</td>
</tr>
<tr>
<td>Positive</td>
<td>106</td>
<td>9016</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>200</td>
<td>9800</td>
<td></td>
</tr>
</tbody>
</table>

At 2% prevalence of glaucoma with IOP > 21 mm Hg
Sensitivity: 47%, Specificity: 92%

Detecting glaucoma at an early stage is ideal, but requires a sensitive and specific test. A test that is highly sensitive (without high specificity) enough to detect early disease usually leads to many false positives. For screening, a test should have a reasonably high sensitivity with as high specificity as possible. Prevent blindness America suggests 95 to 98% specificity and 85% sensitivity for moderate to severe glaucoma. Till date, all the tests available for glaucoma diagnosis does not have high sensitivity and specificity when used alone. If we use combination of these tests, than a good combination of sensitivity and specificity can be achieved.
Myths Generated by Inappropriate Interpretation of Recent RCT's (Randomized Controlled Trials) in Relation to IOP

We would like to address a few statements and concepts that have emerged from the recent RCTs:

1. IOP less than 12 mm Hg on the average has the least risk for glaucoma progression (AGIS).
2. Each mm Hg IOP reduction reduces the risk of glaucoma by 10% (EMGT).

AGIS recommends an IOP below 18 mm Hg through out the follow-up (with a mean IOP of 12.3 mm Hg) to prevent visual field loss. EMGT reported that each mm Hg lowering reduces the risk of field progression by 10%. These two statements are perhaps the most frequently referenced statements from recent RCTs. We would like to present our interpretation and inferences for the statements.

In AGIS, mean and the range of visual field score in the study cohort was 8.8 ± 4.4. We must remember that all this analysis is post hoc analysis. The criterion for visual field progression in this study was defined as “deterioration of visual field by more than 4 score points to be considered significant”. Just go through the Figure 4A. The point to note here is the fact that the upper limit on X-axis is 4 score point, which is just the score of 4 taken to indicate change and hence undue amplification of X-axis. The same figure is reproduced in Figure 4B with the X-axis expanded to the full available AGIS score of 0 to 20. Now the benefit of IOP reduction in the figure is not as significant as it is made out to be and the differences between the groups becomes much more smaller.

By putting forward these interpretations, we do not aim to under estimate the importance of low IOPs for protection of the visual function.

Both OHTS and the EMGT state that each mm Hg lowering of IOP is associated with a 10% lowering of risk. First, we must remember that in both these studies, this conclusion was the result of “post hoc” analyses; such analyses should always be interpreted with great caution. In EMGT, this association was demonstrated using a Cox’s hazard model and the hazard ratio was found to be 1.1. Hazard ratio is like RR and is interpreted in the same manner.

A relative risk of 1.1 is small (large numbers of subjects can make anything statistically significant). If the relative risk is small, (like 1.1), one-way to make it look attractive is to use “excess” risk. The formula for excess risk is RR-1 expressed as a percentage = 1.1-1 = 10%. This derivation (with other assumptions) has probably led to the “10% reduction per mm Hg reduction” interpretation. While it is the truth, the statement is perhaps best interpreted keeping the overall picture in mind.

Table 3 shows do’s and don’t in case of raised IOP.

SUMMARY

Currently, in glaucoma definition, IOP is only causal risk factor and not important for the diagnosis. However, IOP is the only treatable risk factor in the armamentarium for glaucoma management. Nearly, 50% of the patients with glaucoma are normal tension glaucoma and on first evaluation would have IOP less than 22 mm Hg. IOP is a dynamic variable and has temporal and diurnal fluctuations. We need to assess at least diurnal fluctuation in glaucoma.
Table 3: Do’s and don’ts in case of raised IOP

<table>
<thead>
<tr>
<th>Do’s</th>
<th>Don’ts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Try and check IOP with Goldmann applanation tonometry</td>
<td>Do not use digital IOP and try to avoid Schiotz tonometry also</td>
</tr>
<tr>
<td>Repeat IOP; preferably by masked observer</td>
<td>Do not rely on a single IOP value</td>
</tr>
<tr>
<td>Diurnal variation of IOP</td>
<td>Do not use IOP as only criteria for diagnosis</td>
</tr>
<tr>
<td>Gonioscopy: Very important for diagnosis of PAC (primary angle closure), PACG (primary angle closure glaucoma) and some forms of secondary glaucoma like angle recession glaucoma</td>
<td></td>
</tr>
<tr>
<td>Rule out secondary glaucoma like pseudoexfoliation glaucoma, pigmentary glaucoma</td>
<td></td>
</tr>
</tbody>
</table>

patients. IOP is an important clinical tool for glaucoma management, however screening for glaucoma with IOP measurement will lead to very high false positives.

REFERENCES

5. Heijl A, Leske MC, Bengtsson B, Hyman L, Bengtsson B, Hussein M. Early manifest treatment trial group; Early manifest glaucoma trial group. Reduction of intraocular pressure and glaucoma progression: Results from the early manifest glaucoma trial. Arch Ophthalmol. 2002;120:1268-79.

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