
THE UPPER LIMIT OF INDIVIDUAL NORMAL RANGE OF INTRAOCULAR PRESSURE – A PERSONALIZED CRITERION FOR IOP EVALUATION

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Objective — to determine clinical value of the use of the upper limit of individual normal range of intraocular pressure (IOP) in glaucoma diagnosing. **Materials and methods.** The study enrolled 229 conditionally healthy participants (229 eyes) with no ocular complaints after a basic ophthalmic assessment. Ocular blood flow and IOP were measured with Ocular Blood Flow Analyzer (Paradigm Medical Industries). An original formula was further used for calculation of the upper limit of normal range of IOP. All patients were divided into two groups depending on whether or not their IOP fell within the statistically normal range, i.e. was less than 21 mmHg. Thus, group 1 included 193 patients (193 eyes) with IOP from 6.7 to 21.0 mmHg, group 2 — 36 patients (36 eyes) with IOP from 21.7 to 30.8 mmHg. Glaucoma diagnosis was made from automated perimetry (Humphrey Visual Field Analyzer) and retinal tomography (HRT3, Cirrus HD-OCT) findings. **Results.** In group 1, the IOP was found to exceed the upper limit of individual normal range in 38 eyes, thus indicating the probability of glaucoma; of them, in 23 patients (60.5%) the diagnosis was confirmed by further examinations. In the rest 155 eyes from group 1 the IOP matched the individual normal range; of them, glaucoma was ruled out in 154 eyes (99.35%). In group 2, a risk of glaucoma was determined in 27 eyes, of which 24 (88.9%) were further diagnosed. In 9 eyes the IOP exceeded the statistically normal values and yet was within the individual normal range. In none of those 9 cases glaucoma was found. **Conclusion.** The upper limit of individual normal range of IOP is a personalized diagnostic criterion, which is more significant for evaluation of the risk of having or developing glaucoma than the upper limit of statistically normal range (21 mmHg).

Key words: risk of glaucoma, intraocular pressure, target pressure, tolerable pressure, glaucomatous optic neuropathy.

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INTRODUCTION

The measurement of intraocular pressure (IOP) is the most common way to detect the risk of glaucoma presence in healthy eyes. Nowadays a number of reliable methods of measuring IOP is known and used worldwide [1–5]. However, conventional interpretation of these measurements' results based on universally accepted normal IOP range, with its upper limit of 21 mmHg, may lead to serious mistakes particularly in eyes with normal-tension glaucoma (NTG), as well as in cases of ocular hypertension. In the last 2014 edition of the Definitions and Guidelines for Glaucoma the authors encourage not to be guided by prior generally accepted average normal IOP values in the diagnostics and treatment of glaucoma [6].

In 1960s first indications of the individual character of tolerated intraocular pressure in glaucoma patients begun appearing in scientific literature [7, 8]. In 1975–1991 A.Vodovozov [9–13] suggested for the first time a new individualized approach to IOP assessment, i.e. the method of determining tolerable pressure in eyes with glaucoma. The author assessed the level of IOP that provided maximum improvement of perimetric and electrophysiological data in glaucomatous eyes, while gradually reducing excessive IOP with osmotic hypotensive medication. The assessed optimal level of eye pressure was defined as “tolerable pressure” (TP). Several other researchers suggested determining tolerable pressure in eyes with glaucoma by assessing hemodynamic changes during the stress-relief

test IOP reduction [14, 15] or, on the contrary, compression-induced ocular hypertension [16].

While the significance of these attempts to individualize IOP evaluation and the objectivity of their underlying principles should be acknowledged, they can hardly be used in wide practice due to their extreme complexity.

Later on “tolerable pressure” was substituted in ophthalmological literature by “target pressure” — a term bearing the same meaning, but more widely known till the present day. So called calculation methods were suggested for defining it [17–23]. A part of these methods is based on complex formulas that take into consideration such presumably significant criteria as sex, race, age, refraction, blood pressure, glaucoma stage, glaucomatous optic neuropathy progression rate etc. Other methods are simply reduced to a recommended decrease of 20–40% of existing IOP. Therefore, it would seem fair to question the objectivity and effectiveness of said calculations [24, 25].

Recently we have reported on an original concept of acquiring the personal ocular pressure upper limit (POPUL), referred to in these articles as “tolerable intraocular pressure” (tIOP) [26, 27]. POPUL calculation formula uses volumetric ocular blood flow (OBF) data as its basic variable. The study obtained a regression curve of negative correlation between OBF and the axial length (AL) of the eye. The curve was subsequently used as a nomogram to derive the OBF norm for each value of the AL. The derived variable was then entered into the POPUL calculation formula. According to the concept, each eye has a

definite individual IOP norm value. Furthermore, eye pressure upper limit can be either much lower or, on the contrary, higher than 21 mmHg both in healthy and glaucomatous eyes. At the same time, due to compensatory mechanisms of the eye, a certain mild elevation of IOP over POPUL level may still not cause any detectable optic nerve damage.

The present study includes clinical material, gained since the first results of POPUL investigation were published. A new statistical analysis of overall data was also performed to evaluate the validity of the method for determining POPUL in healthy eyes, taking into account the extended clinical experience.

The aim of the study was to evaluate the clinical relevance of personal ocular pressure upper limit as a personalized criterion of IOP assessment in glaucoma diagnostics.

Materials and methods

the study included a total of 229 individuals aged from 16 to 87 years with no ophthalmological complaints, who applied for routine checkup. All ocular pathology that could lead to non-glaucoma related morphofunctional changes in the optic nerve was excluded during the course of the study. Only one randomly chosen eye per subject was included into the study. The patients were divided into two groups according to statistically normal or excessive IOP (>21.0 mm Hg) respectively. OBF was measured using the Ocular Blood Flow Analyzer (OBFA) (Paradigm, USA), which is known to simultaneously provide an IOP measurement that is equivalent to Goldman tonometry. All subjects were informed about the study procedure and consented to participate. The study was approved by the local ethics committee.

The exclusion criteria were as follows: presence of inflammatory eye diseases, corneal pathology, history of a previous eye surgery, carotid artery stenosis (diagnosed or operated), arrhythmia, nystagmus and poor visual fixation that could present with artifacts during the blood flow analysis.

In all cases POPUL value was calculated using the following formula:

$$\text{POPUL} = \text{IOP} \times \text{OBF} / \text{OBF}_{\text{norm}}$$

where IOP – intraocular pressure (mmHg), OBF – ocular blood flow (mL/sec), OBF_{norm} – ocular blood flow norm (mL/sec).

IOP and OBF values were obtained from the OBFA examination protocol. OBF_{norm} value was derived from the regression dependence curve nomogram according to the AL of the eye (Fig. 1). The curve is described mathematically as follows: $\text{OBF}_{\text{norm}} = 6.58 \times 10^5 \times \text{AL}^{-3.316}$; $R^2=0.40$ (R – approximation coefficient; $p<0.005$).

AL was measured by means of Alcon's Ocuscan RxP. The calculations and analysis were performed using specially designed software. An individual IOP scale dis-

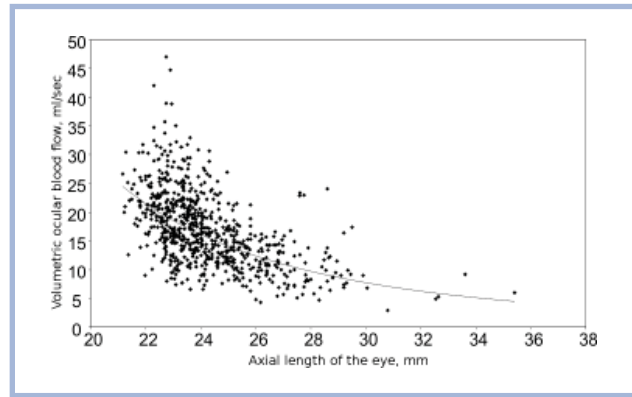


Fig. 1. Negative correlation regression dependence curve, serving as a nomogram for determination of ocular blood flow (OBF) norm value.

played in the research form was composed for each eye (Fig. 2).

The green zone of the scale represents the diapason of IOP individual optimum implying a range of physiological fluctuation of IOP limited by the value of POPUL. The yellow (or buffer) zone reflects an averaged range of acceptable IOP elevation over POPUL level within 5 mmHg, due to compensatory abilities of the eye. The red zone represents unacceptable excess of IOP over the POPUL value. Calculated POPUL value always represents the border between the green and yellow zones, while the actual IOP level may coincide with any point of the scale, depending on how much it exceeds or falls behind POPUL.

The individual IOP scale presents a valuable practical instrument of interpreting the calculated POPUL. In each case POPUL defines the position of the upper border of the green zone, in dependence to which the yellow and red zones are positioned. Therefore, the lay-out of the indication zones will differ for each eye individually.

Interpretation

The resulting data was interpreted based on the experience gained since 2009:

IOP is lower than/coincides with POPUL. This situation is interpreted as no probability of glaucoma presence/development.

IOP is higher than the POPUL value, but is located in the buffer zone. Low to moderate probability of glaucoma presence/development (depending on proximity of IOP location to either green or red zone, respectively) is identified.

IOP is in the red zone. A high probability of glaucoma presence/development is defined.

All 229 eyes involved in the study were subjected to glaucoma diagnostics regardless of whether its probability had been defined or not. Glaucoma was diagnosed by means of gonioscopy, optic nerve head and retinal nerve fiber layer (RNFL) qualitative and quantitative analysis (indirect fundus ophthalmoscopy, confocal scanning la-

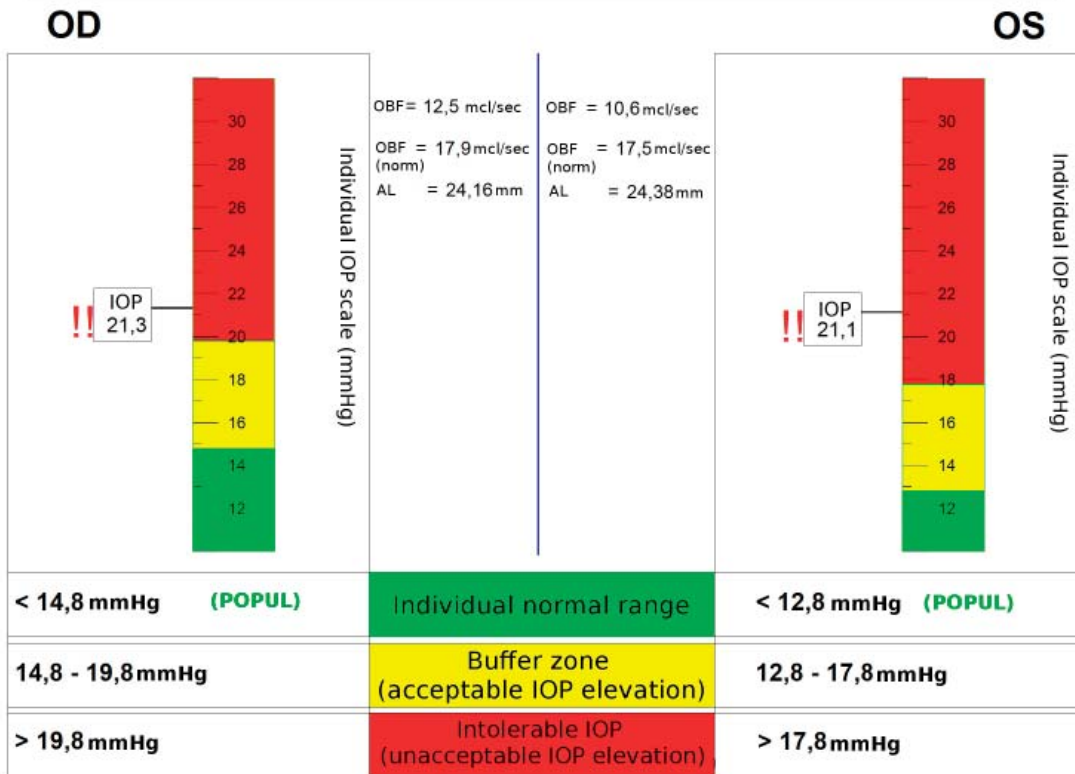


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**Individual intraocular pressure normal range evaluation
Blood Flow Analyzer (Dicon, Paradigm)**

Name: *[blurred]* **Date of birth:** 1934
Sex: male **Examination date:** 08.09.2014



Risk of glaucoma: Absent
 Low
 Moderate
 High

Risk of glaucoma: Absent
 Low
 Moderate
 High

Commentaries:

Physician: *[blurred]*

Fig. 2. Individual IOP scale appearance.

ser ophthalmoscopy HRT3, spectral-domain optical coherence tomography by means of Cirrus HD-OCT), and standard automated perimetry – SAP (Humphrey Field Analyzer – full threshold 30-2).

Statistical analysis

The sensitivity and specificity of the method were calculated with positive and negative predictive values for POPUL and statistical norm of IOP (21.0 mm Hg) for detecting the probability of glaucoma. The difference in the sensitivity and specificity between POPUL and statistical norm of IOP was determined by two tailed exact Fisher's test. The informative value of exceeding both POPUL value ("POPUL – IOP") and the statistical norm of IOP ("21 – IOP") in healthy and glaucomatous eyes was assessed by defining the areas (AUC) under the receiver operator characteristic (ROC) curves. ROC-curve analysis and comparison were performed in Analyze-it application for MS Excel.

Results and discussion

The descriptive parameters of the groups are given in **Table I**.

Group 1 comprised 193 patients (193 eyes) with statistically normal IOP ranging from 6.7 to 21.0 mmHg (mean 14.9 ± 3.5 mmHg). Actual IOP exceeded the POPUL value in 38 eyes by 0.5–12.6 mmHg (mean 4.2 ± 2.8 mmHg). In the course of further investigation, mild to severe stages of open angle glaucoma (OAG) were diagnosed in 23 of those 38 eyes (60.5%). In 155 eyes, the calculated POPUL value appeared to be equal to or higher than actual IOP at the moment of examination by 0.5–8.0 mmHg (mean 2.8 ± 1.9 mmHg). All of these eyes were qualified as having no probability of glaucoma existence. No signs of it were detected in all but 1 eye (0.65%) of a 38 year-old-female, in whom initial primary OAG was finally confirmed. Final interpretation of this case was hindered by the patient's unavailability for further examination and follow-up.

Table I. Demographic profile of the study groups

Demographics	Group 1, IOP ≤ 21.0 mmHg	Group 2, IOP > 21.0 mmHg
Patients (eyes)	193 (193)	36 (36)
Sex, n (%)		
Male	85 (44%)	13 (36%)
Female	108 (56%)	23 (64%)
Age, n (Mean ±SD*)		
≤40 years	31 (35.5±4.5)	6 (34±5.3)
>40 years	162 (59.7±10.2)	30 (63±7.5)

*SD – standard deviation

Table II. Probability degrees of glaucoma presence in two study groups

Study group	Probability degree, n (%)			
	No risk	Low	Moderate	High
Group 1, IOP ≤ 21.0 mmHg (n=193)	155 (80.3%)	10 (5.2%)	18 (9.3%)	10 (5.2%)
Group 2, IOP > 21.0 mmHg (n=36)	9 (25%)	3 (8.3%)	2 (5.6%)	22 (61.1%)

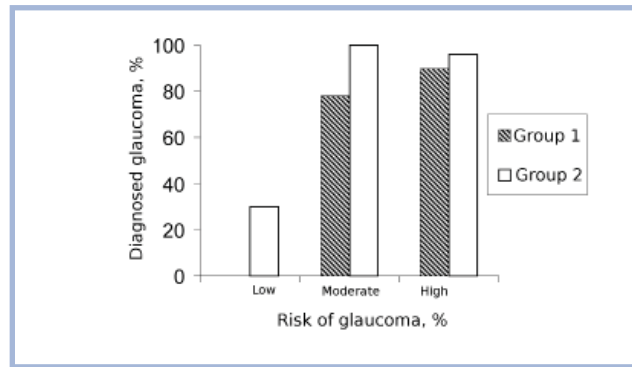


Fig. 3. Glaucoma confirmation rates in eyes with various degrees of risk for glaucoma in two study groups (Group 1 – 193 eyes with statistically normal IOP ≤ 21.0 mmHg, Group 2 – 36 eyes with excessive values of IOP > 21.0 mmHg).

Group 2 comprised 36 patients (36 eyes) with excessive values of IOP between 21.7 and 30.8 mmHg (mean 23.4 ± 2.4 mmHg). In 27 eyes the actual IOP was higher than POPUL by 1.1–16.2 mmHg (mean 7.6 ± 3.9 mmHg). Mild to severe stages of POAG were diagnosed in most of the cases – 24 eyes (88.9%). In the remaining 9 eyes actual IOP, though exceeding the statistical norm, turned out to be below POPUL by 1.0–4.4 mmHg. None of these eyes showed any morphofunctional evidence of glaucoma during further investigation.

The rates of various identified degrees of probability of glaucoma existence/development are shown in **Table II**.

Figure 3 presents the correlation between the confirmation of glaucoma diagnosis and various prior degrees of its determined probability.

A comparative analysis of sensitivity and specificity of actual IOP relation to both POPUL and the statistical norm was conducted in order to assess the informativeness of the new method. A significant difference in sensitivity was found between POPUL and the statistical norm of IOP as the criteria for detecting possible existence of glaucoma – 98% and 51% respectively ($p < 0.05$ for two

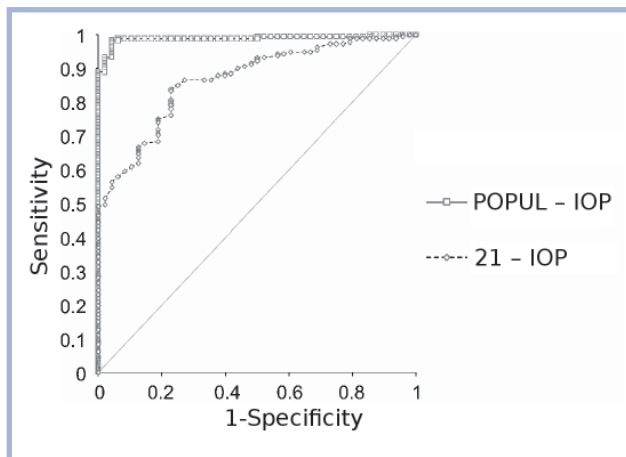


Fig. 4. The receiver operator characteristic curves for the excess of POPUL value and the excess of statistical norm of IOP in healthy and glaucomatous eyes.

tailed exact Fisher's test). No significant difference was determined in their specificity for glaucoma detection – 90% and 93% respectively ($p=0.2563$). The positive predictive value was determined as 72% for POPUL, and 67% for the statistical norm of IOP. The negative predictive value was 99% for POPUL and 88% for the statistical norm of IOP. The AUC, presented in **Figure 4**, was significantly higher ($p<0.005$) for “POPUL – IOP” index (0.99) than for “21 – IOP” index (0.87).

Although glaucoma evidently has multifactor etiology and pathogenesis, many of the researchers consider that elevated IOP plays a primary role in the development and progression of glaucomatous optic neuropathy [28–33]. At the same time, it seems obvious that statistical upper limit of IOP (21 mmHg) may not satisfy today as a reference point in glaucoma diagnostics and monitoring, considering primarily the current dramatic increase in the prevalence of NTG throughout the world. In the meantime all currently known methods of individualized IOP assessment and defining target pressure are either too complex for practical application or too inefficient due to insufficient objectivity of their calculation principles.

The calculation of POPUL as a personalized criterion of ocular tonus evaluation is based on measuring OBF by means of Ocular Blood Flow Analyzer – OBFA. In previous studies of other authors [35], the absence of the established criteria of OBF norm alongside a wide range of its normal values in healthy eyes limited the clinical and diagnostic value of OBFA-acquired OBF values for glaucoma patients. Although the difference between the value of OBF in patients with POAG and normal control groups was statistically significant, OBF is not suitable to serve as a diagnostic criterion to distinguish POAG and absence of glaucoma, due to its low sensitivity and specificity [36, 37]. The nomogram we derived in the course of our study is basically an explanation and a solution of the problem of wide range of normal OBF values and the ab-

sence of criteria of the said norm. As a result, the nomogram served as a center piece of the suggested POPUL calculation, that allowed the use of OBF values as an indicator of IOP deviation. Low OBF could point at the excessive level of IOP even if it is lower than 21 mm Hg, and vice versa, high or normal OBF values may indicate no overpressure regardless of the actual IOP value.

In the first group of this study, glaucoma was diagnosed in more than 60% of the eyes with statistically normal IOP, which nevertheless showed a moderate to high risk of glaucoma presence due to exceeding of their POPUL value. Glaucoma diagnosed in these individuals would normally be classified as normal or low-tension glaucoma, which in turn would present a terminological contradiction since the statistical IOP norm could not be considered normal for these eyes, as it substantively exceeded their individual ocular pressure norm.

It is evident that in Group 2 the suspicion of glaucoma presence was based on the actual IOP being over 21 mHg. As it turned out, in 9 of these eyes the actual IOP was still below the POPUL value. No signs of glaucoma were found in these eyes during further investigation. These cases could be qualified as essential hypertension. At the same time by analogy with the “normal-tension” glaucoma in the previous group, the term “ocular hypertension” seems equally out of place here, since actual IOP values of the patients in question lay well below their personal norm. Other eyes in Group 2 with various defined risks of glaucoma existence or development did indeed present with glaucoma in around 90% of the cases.

As seen in the diagram, presented in Figure 3, glaucoma was diagnosed in about 80% of “moderate risk” cases and in more than 90% of “high risk” eyes similarly in both groups. This clearly shows that the probability of glaucoma is strongly dependent on how prominent is the exceeding of POPUL, in fact regardless of whether the existing IOP is statistically normal or above 21 mm Hg. The absence of glaucoma signs in eyes that presented with buffer-zone elevation over POPUL values can be explained by a slow development of glaucomatous optic neuropathy in the early stages of the disease. This also explains the cases in which glaucoma risks defined during POPUL calculation were not confirmed by following diagnosis establishment. In these cases we recommend, firstly, to repeat the POPUL calculations in order to exclude possible artifacts and calculation errors, and, secondly, a follow-up for these patients, even if the detected risk was qualified as low and no signs of glaucomatous optic neuropathy were detected.

Conclusion

The inadequacy of the statistical IOP norm as the assessment criterion is possibly one of the main reasons for current conflicting data and ongoing discussions about the role of IOP in the development and progression of glaucoma. Giving due credit to the existing theories of

glaucoma pathogenesis including normal-tension glaucoma, one should note that neither of them suggests the possibility of a natural individual IOP norm existence. In the meantime, the data that was accumulated during our eight-year study of individual IOP characteristics in the Scientific Research Institute of Eye Diseases suggests that personal eye pressure norm presents an essential physiologic factor, determining the critical level of IOP for any eye, exceeding of which becomes one of the main links in the pathogenetic mechanism of the glaucomatous optic neuropathy. This concept could evidently shed light on one of the most challenging problems of modern ophthalmology: why glaucoma (normotensive) in 30—

50% of all cases is developed in the eyes with IOP below the statistic norm of 21 mmHg, and doesn't develop with IOP well above the statistical norm in some eyes with essential hypertension.

Our data proves validity and high informative value of the tested method for POPUL assessment, which appears to represent a new important criterion to adequately evaluate existing IOP. The most important advantage of the new method, distinguishing it from the other individualized approaches to determine the optimal IOP level, is the possibility of its application as a screening diagnostic facility for healthy population for early detection of glaucoma existence or development risk.

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