

TRANSLAMINAR GRADIENT AND GLAUCOMA

SUMMARY

Objective: The cribriform plate is a threshold of the intraocular pressure (VOT) and of the intracranial pressure (IKT). The difference between the VOT and IKT is referred to as translaminar gradient (TLG). The goal was to evaluate the Glaucoma progression (visual field, fundus examination, HRT) with / without topical anti-glaucomatous therapy) in relation to the TLG.

Patients and methods: the significance of TLG has been studied in two groups. I. Group: 57 patients diagnosed and treatment of Primary Open-Angle Glaucoma (PGOU), 10 patients with Ocular hypertension (OH), 7 patients with Normal-Tension Glaucoma (NTG), and 75 healthy without glaucoma. The examinations of TLG were carried out once and retrospectively. In II. group there were prospectively studied 14 patients with OH and 24 patients with newly detected PGOU without local therapy. The examinations were performed 4 times at intervals of 10 to 11 months. All tests included a basic eye examination, ORA tonometry, HRT examination, gonioscopy, Color Doppler sonography of blood vessels of the eye and orbit. Venous pulsation pressure (VPT) has been recorded by the Ophthalmodynamometer Meditron (D-ODM). In case of spontaneous retinal venous pulsation, VPT was considered as the same pressure as the VOT. The TLG was calculated with formula of Querfurth: $ICT = 0.29 + 0.74 (VOT / PI (AO))$. $PI(AO)$ – Pulsatility index of the Ophthalmic artery (AO)]. **Results:** I. group: TLG was in the control group without Glaucoma: 12.2 ± 2.0 torr. The NTG group: 9.0 ± 1.70 mm Hg. PGOU: 11.1 ± 1.91 mm Hg. OH: 12.6 ± 0.85 mm Hg. IKT alone does not show a significant relationship to the presence of glaucoma, ocular hypertension. II. Group: The average TLG in Ocular Hypertension (14 patients) has been 3.8 ± 1.2 torr. 2 patients (OH) had TLG 10 torr. and 15 torr. After 4 years in one of them (TLG = 15 torr.) there was recorded Glaucoma progression. In the PGOU group before antiglaucoma therapy, TLG was 15.0 ± 4.8 torr for all patients. After setting up local anti-glaucoma therapy and decreasing VOT, the TLG in 20 patients reduced to 3.6 ± 1.3 mm Hg.

Conclusion: TLG showed a significant relationship to the Glaucoma progression. The risk of glaucomatous damage increases proportionally with increasing Translaminar gradient. Translaminar gradient can be used to refine the so-called. "Target VOT". TLG has a role in ocular damage (ocular hypertension, glaucoma, vascular occlusion, optic neuropathy), intracranial damage, orbitopathy, selection of appropriate antiglaucomatous therapy.

Key words: color Doppler ultrasonography, glaucoma, ocular hypertension, ophthalmodynamometry, translaminar gradient, venous pulsation pressure, venous pulsation.

Čes. a slov. Oftal., 73, 2017, No. 2, p. 52–56

Čmelo J.

Center for neuro-ophthalmology,
Bratislava,
Head doc. MUDr. Jozef Čmelo, Ph.D., MPH

The authors of the study declare that no conflict of interest exists in the compilation, theme and subsequent publication of this professional communication, and that it is not supported by any pharmaceuticals company.



Doc. MUDr. Jozef Čmelo, Ph.D., MPH
Centrum neurooftalmológie
Škultétyho 1
831 03 Bratislava, SR
e-mail: palas.ey@gmail.com

INTRODUCTION

Glaucoma is the most common cause of blindness worldwide. It is characterised by a progressive degeneration of the optic neurons in the optic nerve and in the brain. At present the most significant risk factor is intraocular pressure (IOP). With regard to the fact that glaucomatous changes occur also in patients with "physiological" intraocular pressure, it is evident that other risk factors also play a role. One of these is the difference in the region of the lamina cribiformis (LC). The lamina cribiformis is the threshold of 2 pressure spaces: the intraocular space, with its IOP, and the subarachnoid space, with intracranial pressure (ICP). The difference between IOP and ICP is referred to as the translaminar gradient (TLG).

The objective was to observe signs of glaucoma progression in the visual field, fundus examination and HRT examination with / without local anti-glaucomatous therapy in relation to TLG.

Patients and methodology

Evaluation of the significance of the translaminar gradient in glaucoma was examined in two groups.

Group I:

- Retrospective evaluation of 57 patients with already diagnosed and treated open-angle glaucoma, 10 patients with ocular hypertension, 7 patients with normal-tension glaucoma and 75 probands without symptoms of glaucomatous damage.
- In group I the examination was performed once

Group II:

- Prospective observation of 14 patients with ocular hypertension and 24 patients with newly detected primary open-angle glaucoma (POAG) without any applied local therapy. Patients with endocrine orbitopathy or lesion in the intracranial space were excluded from the groups. Due to potential changes of the biochemical properties of the lamina cribiformis, pigment and pseudoexfoliative glaucoma were excluded from the observation.
- In group II a total of four examinations were conducted at an interval of 10-11 months. The examinations were conducted in the period of 2009-2015.

All the examinations contained: central vision; contrast sensitivity; visual field 30-2 threshold: index PSD – pattern

standard deviation, or accepted falsely (+) errors > 5% and false (-) errors > 20%; intraocular pressure (applanation with conversion of pachymetry, ORA system); gonioscopy; biomicroscopic examination of anterior and posterior segment; HRT examination (C/D: area ratio, rim area: mm², rim volume: mm³); examination of through-flow parameters (arteria / vena centralis retinae, arteriae ciliares posteriores, arteria ophthalmica, vena orbitalis superior) with the aid of colour Doppler sonography. Pulsating venous pressure (PVP) was recorded by a digital ophthalmodynamometer Meditron (D-ODM). In the case of spontaneous venous pulsation of the vena centralis retinae, PVP was considered to represent pressure equal to IOP. TLG was calculated according to the Querfurth formula: $ICP = 0.29 + 0.74 (IOP / PI (AO))$. The pulsatility index (PI) was recorded from the through-flow parameters in the arteria ophthalmica (AO).

RESULTS

Group I:

The average approximate values of intracranial pressure in the individual sub-groups is illustrated by table 1. ICP alone does not manifest a significant relationship to the presence of glaucoma or ocular hypertension. Significant changes in relation to the individual sub-groups were demonstrated only by the translaminar gradient (table 2).

Group II:

In the patients in whom ocular hypertension was demonstrated after 36-45 months of observation, in 12 cases TLG was on average 3.8 ± 1.2 torr, 2 patients from the original group of assumed ocular hypertension had TLG 10 torr and 15 torr. In one of these (TLG = 15 torr), glaucoma progression was recorded after 4 years.

In the POAG group (24 patients), TLG was 15.0 ± 4.8 torr in all patients. After the application of local anti-glaucomatous therapy and the adjustment of IOP, TLG was reduced in 20 patients to 3.6 ± 1.3 torr. In 4 patients progression of glaucoma was recorded, even though IOP was reduced to the values of 16-18 torr. TLG was 11-13 torr. After a further reduction of IOP to values of 10-12 torr with TLG of 4-7 torr at an interval of 12 months, further progression of glaucoma was not observed.

DISCUSSION

At present a wide spectrum of precise diagnostic instruments, methods and sophisticated diagnostic procedures are available for the diagnosis of glaucomatous damage

(1, 2, 3, 6, 7, 8, 10, 14, 15, 17). Despite this, there are still patients in whom it is difficult to determine early glaucoma progression. The translaminar gradient has shown itself to be a further piece of the mosaic of glaucoma diagnosis. A number of experimental and clinical studies unequivocally confirm the relationship between intracranial pressure and the progression of glaucoma (4, 12, 16, 18). For example, Yablonsky (21) experimentally reduced intracranial pressure in cats, and at the same time reduced intraocular pressure in only one eye. After 3 months he observed a deterioration of the optic nerve where the intraocular pressure was not reduced.

Intraocular pressure is a variable quantity. According to the experience of the author, examination by D-ODM should be performed primarily before other examinations with pressure acting on the eyeball: applanation tonometry, gonioscopy, direct panfundoscopy, as well as e.g. massage of the eyeball. If pressure is exerted on the eyeball directly before examination by D-ODM, the subsequent D-ODM values show a lower SVP value. This applies less often and less pronouncedly upon examination by D-ODM in the other eye. This could be explained by the wide range of TLG values in healthy individuals, or by ocular hypertension. It appears that increased intracranial pressure acts as a partial protective factor against the occurrence of glaucoma. For assessment of the progression of glaucoma, of fundamental importance is the difference between IOP and ICT = TLG (translaminar gradient). The calculation of TLG is possible by a number of methods (table 3). Spontaneous venous pulsation (SVP) is also considered a risk factor in glaucoma. At the same time, however, the absence of SVP has a low prevalence in glaucoma patients in comparison with people without glaucomatous damage (13). In the case of spontaneous venous pulsation of the vena centralis retinae it is possible to consider PVP to be equal to IOP (12).

Glaucoma involves not only affliction of the optic nerve, but the entire ocular system – changes in collagen of the LC, the cornea, sclera, changes in the retina and choroidea, and in the brain tissue. With regard to the topography of the lamina cribiformis and the surrounding tissue, it shall be necessary in future to take into account not only TLG but also the biomechanical properties of the lamina cribiformis (LC), mater pia and subarachnoid space (11). A relationship has been demonstrated experimentally between the pressure in the subarachnoid space and intracranial pressure. Lower pressure than the actual intracranial

Table 1

Average values of intracranial pressure	
Control group – without glaucoma	12.2 ± 2.0 torr
Normal-tension glaucoma	9.0 ± 1.70 torr
Primary open-angle glaucoma	11.1 ± 1.91 torr
Ocular hypertension	12.6 ± 0.85 torr

Table 2

Translaminar gradient	TLG = IOP – ICP
Control group – without glaucoma	2.5 ± 2.1 torr
Primary open-angle glaucoma	12.5 ± 4.1 torr
Ocular hypertension	2.1 ± 1.7 torr

TLG: Translaminar gradient, IOP: intraocular pressure, ICP: intracranial pressure

pressure has been measured in the subarachnoid space. However, when ICP decreased, pressure in the subarachnoid space decreased to an equal extent. This equal reduction was only up to a certain value – the “critical point”. After this point pressure in the subarachnoid space no longer decreased, even despite a further reduction of ICP (5).

It is assumed that ICP does not only have a biomechanical relationship to the progression of glaucoma. Biochemical changes of the coeliolymph have also been demonstrated. Upon higher ICP there is faster production of the coeliolymph, and thus also faster renewal thereof. This leads to better removal of metabolic toxic products (e.g. β -amyloid). β -amyloid is a metabolic toxic product which is located both in the ganglion cells of the retina (experimentally induced glaucoma in animals) and for example in plaques in the case of Alzheimer's disease. For these reasons some authors understand glaucoma as an imbalance between the production and washing out of neurotoxins, similarly as in the case of Alzheimer's disease. The hypothesis of the biomechanical and biochemical mechanism of origin of glaucoma is supported by statistical data: the relatively higher percentage of glaucoma in patients with Alzheimer's disease (AD) in comparison with the population without AD, and at the same time the absence of ocular hypertension in patients with AD. These observations uncover new possibilities in the treatment of glaucoma, for example by means of substances which increase through-flow/renew coeliolymph (18).

TLG may also be significant in the selection of anti-glaucomatous agents. While prostaglandin analogues reduce IOP, β -adrenergic antagonists reduce IOP + worsen perfusion during the night through a reduction of blood pressure, and α_2 -adrenergic antagonists reduce IOP and neuroprotective action. The production of coeliolymph is also influenced by carboanhydrase. As a result, carboanhydrase inhibitors not only reduce IOP, but also reduce ICP. This is suitable for use in conditions with increased ICP and also intraorbital pressure (obesity, endocrine orbitopathy, certain brain tumours, aneurysms etc.).

CONCLUSION

I. The risk of glaucomatous damage increases in direct proportion to the increasing value of the translaminar gradient.

- High intraocular pressure (ocular hypertension, glaucoma)

- Low intracranial pressure (physiological, blockade of coeliolymph etc.)
- The higher the TLG, the greater the probability of glaucoma progression

II. The translaminar gradient serves for specifying the “target” intraocular pressure for the individual patient.

III. Evaluation of TLG is significant upon:

- Ocular changes (ocular hypertension, glaucoma, vascular occlusion, venostasis, neuropathy of optic nerve).
- Intracranial processes (brain tumours, pseudotumour cerebri, hydrocephalus etc.)
- Intraorbital changes (endocrine orbitopathy, endophthalmos, tumours)
- Selection of suitable anti-glaucomatous agent.

Abbreviations

AD – Alzheimer's disease

D-ODM – digital ophthalmodynamometry

CDU – colour Doppler ultrasonography

ICP – intracranial pressure

LC – lamina cribiformis

POAG – primary open-angle glaucoma

SVP – spontaneous venous pulsation

TLG – translaminar gradient

IOP – intraocular pressure

PVP – pulsating venous pressure (venous outflow pressure – retinal venous pressure).

Table 3 Calculation of translaminar gradient

• Measurement of ICP:

- Direct neurosurgical approach:

- Transcranial.
- Lumbar puncture.

- Indirect ophthalmological approach:

- Digital ophthalmodynamometry.
- Transcranial duplex ultrasonography.
- Monitoring of parameters of retinal veins.
- Calculation of ICP according to various formulae:

- $ICP = 0.55 \times BMI \text{ index (kg/m}^2) + 0.16 \text{ KTD (mmHg)} - 0.18 \times \text{age (years)} - 1.91 \text{ (10)}$ (KTD – diastolic blood pressure, BMI – Body mass index)..

- $ICP = 16.95 \times OSASW09 + 0.39 \times BMI + 0.14 \times TKS - 20.90 \text{ (25)}$. OSASW095: width of orbital subarachnoid space at distance of 9 mm behind eyeball (examination of nuclear magnetic resonance). BMI: Body mass index. TKS: median arterial pressure (20).

• Venous pressure (VP)

- $VP = IOP - PVP$ (increase of PVP is linked with glaucoma risk. VP: Venous pressure, IOP: Intraocular pressure, PVP: Pulsating venous pressure).

LITERATURE

1. Čmelo, J., Strmeň, P., Krásnik, V.: Hodnotenie krvného toku v niektorých cievach oka a očnice farebnou dopplerovskou ultrasonografiou. *Čes a Slov Oftal*, 1996, 6, 372–379.
2. Ferková, S., Chynoranský, M., Terek, M.: Hodnotenie progresie glaukómového ochorenia pomocou HRT II (Heidelberg retina tomograph) – výsledky. *Čes a Slov Oftal*, 63(4), 2007: 230–242.
3. Furdová, A.: Zobrazovacie metódy v oftalmológii. Kapitola v skriptách: Slobodníková, Furdová, Králík, Šramka: Moderné zobrazovacie, diagnostické a liečebné metódy. VŠ sv. Alžbety, Bratislava, 2012. ISBN 978-80-89464-18-8 (EAN 9788089464180), s. 64–91.
4. Harris, A., Siesky, B., Wirosko, B.M.: Cerebral Blood Flow in Glaucoma Patients. *J Glaucoma*. PMC [online]. 2013 22(5) [cit. 2016-5-12]. Dostupné na WWW: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4030418/?report=classic>.
5. Hou, R., Zhang, Z., Yang, D., Wang, H.; Chen, W., Li, Z., Sang, J., Liu, S., Cao, Y., Xie, X., Ren, R., Zhang, Y., Sabel, B.A., Wang, N.: Intracranial pressure (ICP) and optic nerve subarachnoid space pressure (ONSP) correlation in the optic nerve chamber: the Beijing Intracranial and Intraocular Pressure (iCOP) study *Brain Res*, 1635, 2016: 201–208.
6. Húšková, D., Čmelová, E., Hradečná, Z., Čmelo, J.: Vytvorenie dotazníka pre lekársku ambulanciu. *Zdravotníctvo a sociálna práca, vedecký časopis*, 8(3), 2013: 18–26.
7. Krásnik, V.: Diabetes mellitus, diabetická retinopatia, gravidita a glaukóm, *Forum Diab*, 2(3), 2013: 163.
8. Kuběna T., Klimešová K., Kofroňová M., Černošek P.: Digitální snímky vrstvy nervových vláken sítnice u zdravého oka a u glaukomu. *Čes a Slov Oftal*, 65(1), 2009: 3–7.
9. Lee, SH., Kwak, SW., Eun Min Kang, Gyu Ah Kim, Sang Yeop Lee, Hyoung Won Bae, Gong Je Seong, Kim, CHY.: Estimated Trans-Lamina Cribrosa Pressure Differences in Low-Teen and High-Teen Intraocular Pressure Normal Tension Glaucoma. *PloS One* [online]. 2016 11(2) [cit. 2016-5-12]. Dostupné na WWW: <http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0148412>.
10. Machalová, S., Čmelová, E., Ďurovčíková, D., Pechová, M., Hikkelová, M.: Intrafamiliárna fenotypová variabilita klasického Marfanovho syndrómu. *Čes Slov Pediat*, 70(5), 2015: 287–292.
11. Marek, B., Harris, A., Kanakamedala, P.: Cerebrospinal fluid pressure and glaucoma: Regulation of trans-lamina cribrosa pressure. *Br J Ophthalmol*, 98(6), 2013: 721–725.
12. Morgan, VW., Balaratnasingam, CH., Lind, ChRP, Colley, S., Kang, MH., House, PH., Yu, DY.: Cerebrospinal fluid pressure and the eye. *Br J Ophthalmol*, 100, 2016: 71–77.
13. Morgan, WH., House, PH., Hazelton, ML., Betz-Stablein, BD., Chauhan, BC, Viswanathan, A., Dao-Yi Yu.: Intraocular Pressure Reduction Is Associated with Reduced Venous Pulsation Pressure. *PLoS One* [online]. 2016 11(1) [cit. 2016-5-12]. Dostupné na WWW: <http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0147915>.
14. Pinto, L., Vandewalle, e., De Clerck, e., Marques-Neves, c., Stalmans. I.: Lack of spontaneous venous pulsation: possible risk indicator in normal tension glaucoma? *Acta Ophthal*, 91(6), 2013: 514–520.
15. Praženicová, M.: Diabetes mellitus a glaukóm. *Forum Diab*, 2(3), 2013: 189–191.
16. Querfurth HW, Arms SW, Lichy CM, Irwin WT, Steiner T: Prediction of intracranial pressure from noninvasive transocular venous and arterial hemodynamic measurements: a pilot study. *Neurocrit Care*, 1(2), 2014: 183–194.
17. Siaudvytyte, L., Januleviciene, I., Ragauskas, A., Bartusis, L., Siesky, B., Harris, A.: Update in intracranial pressure evaluation methods and translaminar pressure gradient role in glaucoma. *Acta Ophthalmol*, 93(1), 2015, 9–15.
18. Výborný P., Dohnalová P.: Využití Heidelbergského retinálního tomografu v prevenci glaukomu. *Čes a Slov Oftal*, 62(1), 2006: 53–58.
19. Wostyn: Fast circulation of cerebrospinal fluid: an alternative perspective on the protective role of high intracranial pressure in ocular hypertension. *Clin Exp Optom*, 99(3), 2016: 213–218.
20. Xie, X., Zhang, X., Fu, J., Wang, H., Jonas, JB, Peng, X., Tian, G., Xian, J., Ritch, R., Li, L., Kang, Z., Zhang, S., Yang, D, Wang, N.: Noninvasive intracranial pressure estimation by orbital subarachnoid space measurement: the Beijing Intracranial and Intraocular Pressure (iCOP) study. *Crit Care* [online]. 2013 17(4) [cit. 2016-5-12]. Dostupné na WWW: <http://ccforum.biomedcentral.com/articles/10.1186/cc12841>.
21. Yablonski M., Ritch R., Pakorny K.: Effect of decreased intracranial pressure on optic disc. *Invest Ophthalmol Vis Sci*, 18 Suppl., 1979: 165.
22. Zhao, D., Zheng He, Algis J. Vingrys, Bang V. Bui, Christine T. O. Nguyen: The effect of intraocular and intracranial pressure on retinal structure and function in rats. *Physiol Rep* [online]. 2015 3 [cit. 2016-5-12]. Dostupné na WWW: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4562590/> Physiological Reports Published 18 August 2015. Vol 3, No: e12507. Doi 10.14814/phy2.12507.