PAULIUS LUČINSKAS

NEINVAZINĖ GLAUKOMOS DIAGNOSTIKA: NAUJI BIOŽYMENYS IR GYDYMO IDĖJOS

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PAULIUS LUČINSKAS

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Mokslinis vadovas:
prof. dr. Arminas RAGAUSKAS (Kauno technologijos universitetas, technologijos mokslai, matavimų inžinerija, T 010).

Redagavo: anglų kalbos redaktorius dr. Armandas Rumšas (leidykla „Technologija“), lietuvių kalbos redaktorė Aurelija Gražina Rukšaitė (leidykla „Technologija“)

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prof. dr. Renaldas RAIŠUTIS (Kauno technologijos universitetas, technologijos mokslai, matavimų inžinerija, T 010) – **pirmininkas**;
prof. habil. dr. Eugenijus KANIUŠAS (Vienos technologijos universitetas, Austrija, technologijos mokslai, matavimų inžinerija, T 010);
prof. habil. dr. Edmundas ŠIRVINSKAS (Lietuvos sveikatos mokslų universitetas, medicinos ir sveikatos mokslai, medicina, M 001);
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prof. dr. Algimantas VALINEVIČIUS (Kauno technologijos universitetas, technologijos mokslai, elektros ir elektronikos inžinerija, T 001)

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Adresas: K. Donelaičio g. 73-402, Kaunas, LT-44249, Lietuva
Tel. (+370) 608 28 527; el. paštas doktorantura@ktu.lt

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PAULIUS LUČINSKAS

NON–INVASIVE GLAUCOMA DIAGNOSTICS: NEW BIOMARKERS AND TREATMENT IDEAS

Doctoral dissertation
Technological Sciences, Measurement Engineering (T 010)

2023, Kaunas

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Address: K. Donelaičio 73-402, Kaunas, LT-44249, Lithuania
Phone: (+370) 608 28 527; e-mail doktorantura@ktu.lt

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The doctoral dissertation is available on the internet http://ktu.edu and at the library of Kaunas University of Technology (K. Donelaičio 20, Kaunas, LT-44239, Lithuania).

TURINYS

SANTRUMPŲ SĄRAŠAS

AARP – Amerikos pensininkų asociacija
ABP – arterinis kraujospūdis
ALK – Lietuvos sveikatos mokslų universiteto Kauno klinikų Akių ligų klinika
BM – biožymuo
CA – smegenų kraujotakos autoreguliacija
CA_{NTG} – paciento, sergančio normalaus akispūdžio glaukoma, smegenų kraujotakos autoreguliacija
CH – smegenų vandenligė
CPP – smegenų perfuzinis slėgis
CSF – smegenų skystis
DBM – diagnostinis biožymuo
detCA – sutrikusi smegenų kraujotakos autoreguliacija
$detCA_{NTG}$ – sutrikusi paciento, sergančio normalaus akispūdžio glaukoma, smegenų kraujotakos autoreguliacija
ED – endotelio disfunkcija
EOA – akies arterijos ekstrakranijinis segmentas
GL – glaukoma
GCBH – Pasaulinė smegenų sveikatos taryba
highIOP – aukštesnis už normalų (sveiko tiriamojo) akispūdis
HS – sveikas tiriamasis iš kontrolinės grupės
HTG – aukšto akispūdžio glaukoma
IBV – intrakranijinis kraujo tūris
ICP – intrakranijinis slėgis
ICPinv – invaziniu būdu matuojamas intrakranijinis slėgis
ICPnon–inv – intrakranijinis slėgis, matuojamas neinvaziniu būdu
IF – leidinio įtakos faktorius
IOA – akies arterijos intrakranijinis segmentas
IOP – akispūdis
IOP_{HS} – sveiko tiriamojo akispūdis
IOP_{HTG} – aukšto akispūdžio glaukoma sergančio paciento akispūdis
IOP_{NTG} – normalaus akispūdžio glaukoma sergančio paciento akispūdis
KTU – Kauno technologijos universitetas
LC – akytoji plokštelė (lot. *Lamina Cribrosa*)
LCAI – ilgiausias smegenų kraujotakos autoreguliacijos sutrikimo įvykis
$LCAI_{HS}$ – sveiko tiriamojo *LCAI*
$LCAI_{HTG}$ – aukšto akispūdžio glaukoma sergančio paciento *LCAI*
$LCAI_{NTG}$ – normalaus akispūdžio glaukoma sergančio paciento *LCAI*
$LCAId_{HS}$ – sveiko tiriamojo *LCAI* dozė
$LCAId_{HTG}$ – aukšto akispūdžio glaukoma sergančio paciento *LCAI* dozė

$LCAId_{NTG}$ – normalaus akispūdžio glaukoma sergančio paciento *LCAI* dozė
LCCI – akytosios plokštelės kreivumo indeksas
lowICP – žemesnis už normalų (sveiko tiriamo asmens, HS) intrakranijinis slėgis
MBSR – sąmoningumu (angl. *Mindfulness*) paremti streso mažinimo būdai
MPD – portatyvus slėgio reguliatorius
nABP – arterinis kraujospūdis, matuojamas neinvaziniu būdu
nCA – smegenų kraujotakos autoreguliacija, stebima neinvaziniu būdu
nICP – intrakranijinis slėgis, matuojamas neinvaziniu būdu (*ICPnon–inv*)
$nICP_{GL}$ – glaukoma sergančio paciento intrakranijinis slėgis, matuojamas neinvaziniu būdu
$nICP_{HS}$ – sveiko tiriamojo intrakranijinis slėgis, matuojamas neinvaziniu būdu
$nICP_{HTG}$ – aukšto akispūdžio glaukoma sergančio paciento intrakranijinis slėgis, matuojamas neinvaziniu būdu
$nICP_{NTG}$ – normalaus akispūdžio glaukoma sergančio paciento intrakranijinis slėgis, matuojamas neinvaziniu būdu
nIOP – akispūdis, matuojamas neinvaziniu būdu
normICP – normalus (HS) intrakranijinis slėgis
normIOP – normalus (HS) akispūdis
NPH – normalaus slėgio smegenų vandenligė
NTG – normalaus akispūdžio glaukoma
OA – akies arterija
OCT – optinė koherentinė tomografija
ON – akies nervas
ONH – akies nervo galvutė
ONSD – akies nervo apvalkalo skersmuo
Pe – išorinis slėgis, naudojamas neinvaziškai matuojant intrakranijinį slėgį
PM – precizinė medicina
POAG – pirminė atviro kampo glaukoma
SD – standartinis nuokrypis
STMI – Kauno technologijos universiteto Sveikatos telematikos mokslo institutas
TCD – transkranijinis dopleris
TCPG – translaminarinis slėgio gradientas
TOF – ultragarsinio signalo sklidimo laikas
VRx – tūrinis reaktyvumo indeksas
VRx_{HS} – sveiko tiriamojo tūrinis reaktyvumo indeksas
VRx_{HTG} – aukšto akispūdžio glaukoma sergančio paciento tūrinis reaktyvumo indeksas
VRx_{NTG} – normalaus akispūdžio glaukoma sergančio paciento tūrinis reaktyvumo indeksas
PSO – Pasaulio sveikatos organizacija
WoS – Web of science duomenų bazė

LENTELIŲ SĄRAŠAS

PAVEIKSLŲ SĄRAŠAS

1. ĮVADAS

Disertacijos sritis, tipas ir struktūra

Disertacija priklauso medicininių matavimų sričiai. Jos temos apima papildomų biožymenų: žemesnio už normalų intrakranijinio slėgio (*lowICP*) ir sutrikusio smegenų kraujotakos autoreguliacijos statuso (*detCA*) įtraukimo į glaukomos diagnostiką galimybių tyrimą. Disertacijos tipas – holistinė apibendrinanti, keturių publikuotų straipsnių pagrindu:

1. Deimantavicius, M.; Hamarat, Y.; **Lucinskas, P**.; Zakelis, R.; Bartusis, L.; Siaudvytyte, L.; Janulevicienė, I.; Ragauskas, A. **Prospective Clinical Study of Non–Invasive Intracranial Pressure Measurements in Open–Angle Glaucoma Patients and Healthy Subjects**. Medicina (Kaunas). 2020 Nov 30;56(12):664. doi: 10.3390/medicina56120664 [9].

2. Hamarat, Y.; Deimantavicius, M.; Dambrauskas, V.; Labunskas, V.; Putnynaite, V.; **Lucinskas, P**.; Siaudvytyte, L.; Simiene, E.; Stoskuviene, A.; Januleviciene, I.; Petkus, V.; Ragauskas, A. **Prospective Pilot Clinical Study of Noninvasive Cerebrovascular Autoregulation Monitoring in Open–Angle Glaucoma Patients and Healthy Subjects**. Transl Vis Sci Technol. 2022 Feb 1;11(2):17. doi: 10.1167/tvst.11.2.17 [10].

3. **Lucinskas, P**.; Deimantavicius, M.; Bartusis, L.; Zakelis, R.; Misiulis, E.; Dziugys, A.; Hamarat, Y. **Human ophthalmic artery as a sensor for non–invasive intracranial pressure monitoring: numerical modeling and in vivo pilot study**. Sci Rep. 2021 Feb 26;11(1):4736. doi: 10.1038/s41598–021–83777–x [11].

4. Hamarat, Y.; Bartusis, L.; Deimantavicius, M.; **Lucinskas, P**.; Siaudvytyte, L.; Zakelis, R.; Harris, A.; Mathew, S.; Siesky, B.; Janulevicienė, I.; Ragauskas, A. **Can the Treatment of Normal–Pressure Hydrocephalus Induce Normal–Tension Glaucoma?** A Narrative Review of a Current Knowledge. Medicina (Kaunas). 2021 Mar 3;57(3):234. doi: 10.3390/medicina57030234 [12].

Žurnalų leidėjai ir straipsnių bendraautoriai sutiko, kad straipsniai būtų naudojami disertacijoje. Glaukomos diagnostikos papildomų biožymenų tema analizuojama pagal publikuotus straipsnius, iš holistinio apibendrinančio požiūrio taško, pateikiant tikslesnės glaukomos diagnostikos bei gydymo idėjas ir įžvalgas išvadose.

Disertaciją sudaro: įvadas, literatūros apžvalga, 4 straipsnių apžvalga, išvados ir tolesnių tyrimų idėjos, santrauka anglų kalba (*Summary*), literatūros sąrašas, autoriaus CV, su disertacijos tema susijusių straipsnių ir mokslinių konferencijų sąrašas, 4 publikacijų kopijos, padėka; 10 lentelių bei 26 paveikslai.

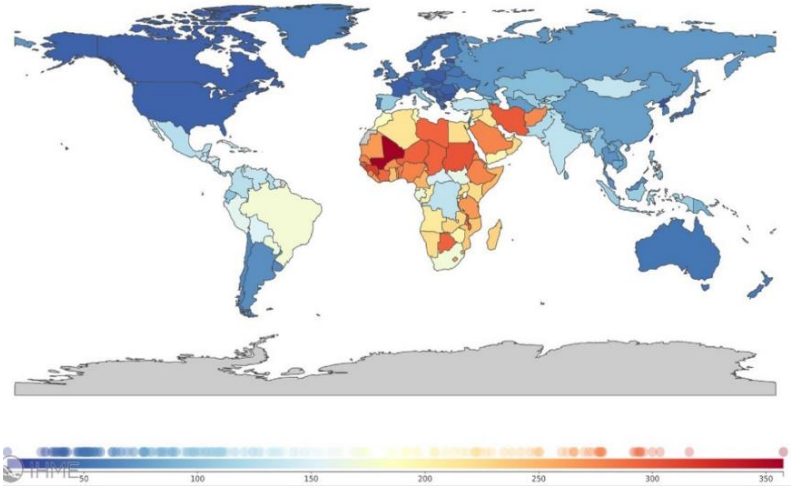
Tyrimų svarba

Rega yra dominuojanti juslė, atliekanti lemiamą vaidmenį žmogaus veikloje, todėl jos sutrikimai turi rimtų pasekmių gyvenimo kokybei. Daugelį jų galima sušvelninti laiku gavus kokybiškos akių priežiūros paslaugas – diagnostiką, gydymą ir reabilitaciją. Akių ligos, tokios kaip, pvz., katarakta, glaukoma (GL) ir kt., gali sukelti regos sutrikimus ir aklumą.

Glaukoma – grupė akių ligų, dėl kurių pažeidžiamas akies nervas, sutrinka rega ir (arba) jis prarandamas; glaukoma yra 2–oji aklumo priežastis po kataraktos ir 1–oji pagrindinė negrįžtamo aklumo priežastis pasaulyje. Aklumas, sukeltas glaukomos, sudaro apie 12,3% [1], o paplitimas pasaulyje tarp 40 metų ir vyresnių pasaulio gyventojų sudaro apie 3–5 % [2].

Pasaulyje glaukoma serga apie 64 mln. žmonių [3], iš jų 6,9 mln. (10,9 %) turi vidutinio sunkumo ar sunkų regos sutrikimą [4]. Pasaulio sveikatos organizacijos (PSO) vertinimu, 2020 m. buvo 76 milijonai 40–80 metų amžiaus žmonių, sergančių glaukoma [5], ir šis skaičius gali padidėti iki 112 mln. iki 2040 m. [1]. Taigi akių priežiūros poreikis pasaulyje smarkiai išaugs ir taps iššūkiu sveikatos sistemoms [5]. 2017 m. duomenimis, daugiausia regos praradimo atvejų dėl glaukomos buvo Afrikoje (1.1 pav.) [6].

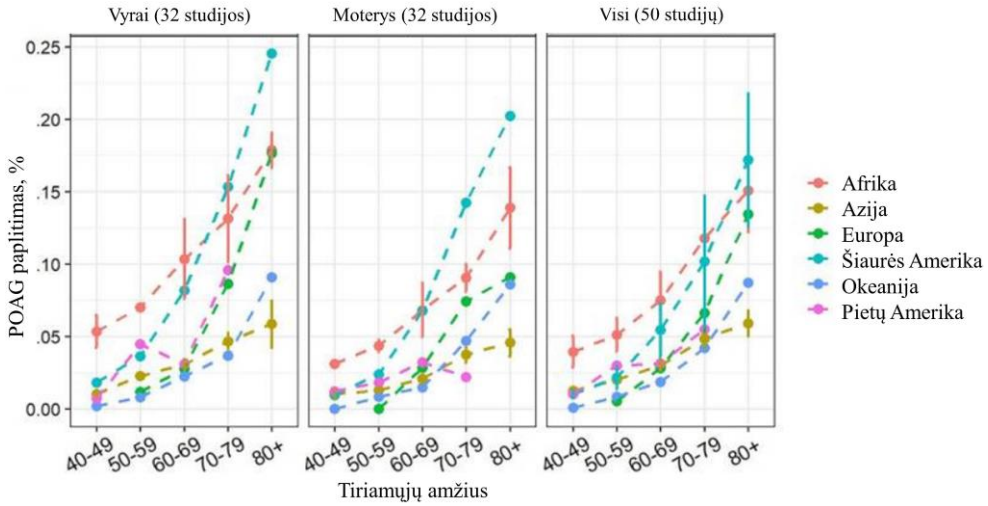
Šiuo metu disponuojamais PSO duomenimis, regos sutrikimai, kuriuos sukelia glaukoma, yra neišgydomi ir negali būti ištaisyti. Tačiau yra veiksmingų gydymo būdų, kurie gali atitolinti arba užkirsti kelią ligos progresavimui, jei ji anksti ir laiku diagnozuojama [5].



1.1 pav. Regos praradimo (dėl glaukomos) atvejų paplitimas pasaulyje.
Spalvomis pavaizduotas atvejų skaičius, standartizuotas pagal amžių, 100 000 gyventojų, 2017 m. duomenys (adaptuota iš [6])

Glaukomos klasifikacijos kriterijų yra daug, svarbiausi iš jų (žr. literatūros apžvalgą) yra šie: glaukoma gali būti pirminė arba antrinė; atviro arba uždaro kampo;

aukšto akispūdžio (HTG) arba normalaus akispūdžio (NTG). Pirminė atviro kampo glaukoma (POAG) yra labiausiai paplitusi pasaulyje, ypač tarp vyresnio amžiaus žmonių (1.2 pav.)



1.2 pav. POAG paplitimas pasaulyje skirtingose amžiaus grupėse, % (adaptuota iš [7])

Neseniai buvo iškelta hipotezė, kad glaukoma gali išsivystyti ir smegenų vandenligės (NPH) gydymo metu [12]. Smegenų vandenligė (CH) apima įvairialypę patologijų grupę, kuriai būdingas nenormalus smegenų skilvelių išsiplėtimas. CH labiausiai paplitusi Azijoje (1.3 pav.) Negydoma CH gali sukelti progresuojantį neurologinį sužalojimą ir mirtį, tačiau, anksti diagnozavus ir atlikus chirurginę intervenciją, simptomai gali visiškai išnykti [8]. Normalaus slėgio CH (NPH) atveju *ICP* neperžengia normos. Disertacijoje nagrinėjamas būtent šis CH tipas.

1.3 pav. CH paplitimas vaikų ir vyresnio amžiaus žmonių populiacijose kartu paėmus (100 000 gyventojų) (adaptuota iš [8])

NPH – būdinga suaugusiems ir geriatriniams pacientams neurologinė liga, kurios simptomai – išsiplėtę smegenų skilveliai, klinikiniai eisenos sutrikimai,

šlapimo nelaikymas, kognityvinių funkcijų pablogėjimas [12]. Populiariausias NPH gydymo būdas – skilvelinis šuntavimas, siekiant pašalinti perteklinį smegenų skystį (CSF). Procedūra atliekama maždaug 5,5 pacientams iš 100 000 gyventojų kasmet. Problema ta, kad šalinant CSF mažėja *ICP*, ir tai kelia glaukomos riziką.

Ši disertacija prisideda prie glaukomos problemos sprendimo globaliu mastu. Joje nagrinėjamos glaukomos diagnostikos, suvaldymo, galimo gydymo (idėjų lygiu) temos, pridedant naujus (papildomus prie jau naudojamų) 2 biožymenis (BM) HTG bei NTG atvejais ir NPH gydymo atvejais.

Mokslinė–technologinė problema

Ar gali technologijų vystymas padėti tobulinti glaukomos (ir jos rizikos) suvaldymą (ar net gydymą), jei pagerinama jos diagnostika, pridedant naujus biožymenis?

Darbinė hipotezė

Glaukomos (ir jos rizikos) suvaldymą (diagnozuojant, pristabdant vystymąsi ir perspektyvoje gydant) gali padėti tobulinti technologijų vystymas, jos diagnostikai suteikiant papildomą vertę pridėjus du naujus biožymenis prie oftalmologijoje įprasto *IOP*:

a) matuojant *nICP* siekiant patikrinti, ar jis yra žemesnis už normalų (*lowICP*, biožymuo Nr. 1), netiesioginiu būdu įvertinant akytosios plokštelės (lot. *Lamina Cribrosa*, LC) deformaciją (ar jos riziką) dėl anormalaus slėgių skirtumo *IOP−ICP*;

b) matuojant *nCA* siekiant patikrinti jos sutrikimą (*detCA*, biožymuo Nr. 2);

c) NPH atveju – patikslinant saugaus žemo *ICP* paradigmą, papildant ją saugaus *ICP* intervalo sąvoka.

Darbo tikslas ir uždaviniai

Darbo tikslas: patikrinti darbinę hipotezę, kad glaukomos suvaldymą galima patobulinti, jos diagnostiką papildžius 2 biožymenimis.

Suformuluoti uždaviniai tikslui pasiekti:

1. Interpretuoti ir apibendrinti HTG sergančių pacientų, NTG sergančių pacientų ir kontrolinės sveikų asmenų (HS) grupių *nICP* vertes, išmatuotas 2 gylių dopleriu (*Vittamed 205*); palyginti rezultatus tarp visų 3 grupių; ištirti *nICP* ilgalaikės stebėsenos galimybes; ištirti papildomo biožymens *lowICP* matavimo įtraukimo į glaukomos diagnostikos procesą galimybes bei glaukomos (ar jos rizikos) suvaldymo tobulinimo galimybes, pasiūlant gydymo idėjas.

2. Interpretuoti ir apibendrinti HTG pacientų, NTG pacientų ir HS grupių *nCA* parametrus, išmatuotus neinvaziniu *CA* stebėsenos metodu, pagrįstu ultragarso

signalo sklidimo smegenyse greičio (*Vittamed 505*) ir arterinio kraujospūdžio matavimais (*Finapres*) ir *CA* parametrų skaičiavimu; palyginti rezultatus tarp visų 3 grupių, įvertinant *CA* sutrikimo mastus; ištirti papildomo biožymens *detCA* matavimo įtraukimo į glaukomos diagnostikos procesą galimybes bei glaukomos (ar jos rizikos) suvaldymo tobulinimo galimybes, pasiūlant gydymo idėjas.

3. Atlikti naratyvinę literatūros apžvalgą NPH gydymo (šuntavimo būdu) metu dėl *ICP* sumažinimo sukeliamos glaukomos rizikos tema; ištirti papildomų biožymenų *lowICP* ir *detCA* matavimų įtraukimo į NPH gydymo procesą galimybes, siekiant patobulinti glaukomos rizikos suvaldymą.

Tyrimų ir straipsnių logika

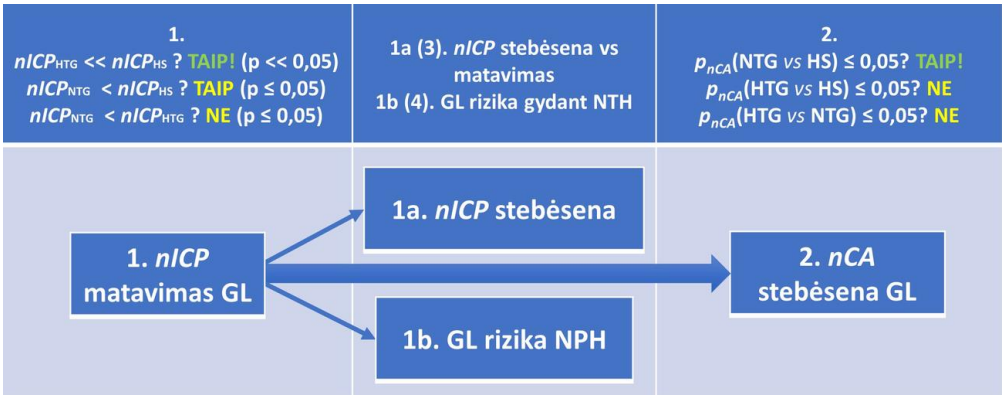
Disertacijoje apžvelgiami tyrimai ir jų pagrindu publikuoti straipsniai logiškai susiję. Vykdant darbo uždavinius, buvo atliktos dvi pagrindinės tyrimų studijos ir dvi papildomos (1.4 pav.). Tiriamųjų suskirstymas į 3 grupes (HTG pacientai, NTG pacientai ir HS tiriamieji) buvo žinomas iš anksto.

1. Siekiant patikrinti darbinės hipotezės a) dalį, buvo suplanuotas GL pacientų *nICP* matavimų perspektyvinis tyrimas [9]. Tyrimo rezultatai parodė, kad nors *nICP* skirtumas lyginant bet kurias 2 grupes statistiškai reikšmingas, HTG ir HS grupių palyginimo rezultatai sufleravo, kad jei HTG atveju *lowICP* gali daryti įtaką HTG vystymuisi (dėl LC pažeidimo), tai NTG atveju, be *lowICP*, gali egzistuoti kitas faktorius, pvz., sutrikusi *CA*.

2. Todėl, siekiant patikrinti darbinės hipotezės b) dalį, buvo atliktas GL pacientų *nCA* stebėsenos perspektyvinis tyrimas [10]. *CA* statusas buvo vertinamas palyginant tūrinio reaktyvumo indekso (*VRx*) ir jo išvestinių *nCA* parametrų reikšmes tarp visų 3 grupių.

3. Papildoma *nICP* modeliavimo ir *in vivo* tyrimų studija [11] atlikta siekiant įvertinti *ICP* cirkadinių svyravimų įtaką bei *nICP* ilgalaikės stebėsenos galimybes.

4. Naratyvinė literatūros apžvalga [12] atlikta siekiant įvertinti glaukomos vystymosi rizikos (dėl *ICP* mažėjimo) idėją normalaus slėgio smegenų vandenligės (NPH) gydymo šuntavimu metu bei *nICP* ir *nCA* matavimo idėją NPH pacientams.



1.4 pav. Tyrimų ir straipsnių logika.
1. Glaukomos (GL) pacientų *nICP* matavimas; 2. Glaukomos pacientų *nCA* stebėsena; 1a (3). *nICP* ilgalaikė stebėsena; 1b (4). Glaukomos rizika gydant NPH šuntavimo būdu

Mokslinis naujumas

1. Pasiūlyti 2 papildomi neinvaziniu būdu matuojami biožymenys, suteikiantys papildomą vertę oftalmologinei ir neurologinei diagnostikai:

1.1. HTG ir NTG atvejais papildomai prie oftalmologijoje naudojamo klasikinio glaukomos biožymens – akispūdžio, viršijančio normalų (*highIOP*), pasiūlyta matuoti *nICP*, patikrinant *lowICP* statusą (naujas BM Nr. 1) ties *Lamina Cribrosa* (LC), siekiant netiesiogiai ištirti anormalaus slėgių skirtumo (*IOP−ICP*) įtaką LC deformacijai; pasiūlytos HTG neinvazinio gydymo idėjos, remiantis LC formos normalizavimu po deformacijos idėja, slėgio fizioterapijos procedūrų, tikslingai atrinktų jogos pratimų bei holistinio požiūrio į smegenų sveikatą pagrindu.

1.2. NTG atveju, be *IOP*, pasiūlyta matuoti *nICP* ir atlikti *nCA* stebėseną, patikrinant *detCA* statusą (naujas BM Nr. 2); pasiūlytos NTG neinvazinio gydymo idėjos, remiantis PSO rekomendacijomis bei holistiniu požiūriu į smegenų sveikatą.

1.3. NPH gydymo atveju papildomai prie naudojamo skilvelinio šunto pasiūlyta matuoti *nICP* ir atlikti *nCA* stebėseną siekiant įvertinti glaukomos riziką ir, esant poreikiui, rekomenduoti pacientams oftalmologinę apžiūrą.

2. Pasiūlyta paradigmų korekcija.

2.1. Glaukomos dabartinė paradigma: glaukoma yra liga, įtakojama vieno slėgio, *highIOP* yra HTG biožymuo, NTG priežastys yra neaiškios; siūloma paradigma: glaukoma yra liga, įtakojama dviejų ar net trijųslėgių, *highIOP* yra HTG biožymuo; *lowICP* yra HTG ir NTG biožymuo; *detCA* yra NTG biožymuo;

2.2. NPH dabartinė paradigma: žema *ICP* vertė yra saugi; siūloma paradigma: per žema *ICP* vertė gali sukelti glaukomos riziką; egzistuoja saugaus *ICP* intervalas, ir būtina kontroliuoti, kad *ICP* vertė neišeitų už jo ribų.

3. Patvirtinta pacientų *nICP* ir *nCA* neinvazinės stebėsenos pakankamu klinikinei praktikai tikslumu galimybė.

Metodai

1. Glaukomos (HTG ir NTG) pacientų bei sveikų savanorių (HS) grupių *nICP* matavimai buvo atliekami 2 gylių dopleriu *Vittamed 205*, sukurtu KTU Sveikatos telematikos mokslo institute (STMI). Pacientus suskirstė į HTG bei NTG grupes LSMU Kauno klinikų Akių ligų klinikos (ALK) specialistai. *nICP* buvo matuojamas ALK kartu su STMI specialistais. Rezultatams apdoroti naudotas *IBM SPSS Statistics software v23.0* programinis paketas.

2. Gaukomos (HTG ir NTG) pacientų bei HS grupių *nCA* stebėsena buvo atliekama naudojant ultragarsinį intrakranijinio kraujo tūrio pokyčių (*IBV*) matuoklį *Vittamed 505* kartu su arterinio kraujospūdžio (*ABP*) neinvaziniu matuokliu *Finapres monitor*. *nCA* sutrikimai buvo vertinami apskaičiuojant *IBV* (apskaičiuojamas matuojant ultragarso signalo sklidimo smegenyse laiką) ir *ABP* lėtųjų bangų koreliacijos koeficientą – tūrinį reaktyvųjį indeksą (*VRx*) bei išvestinius jo parametrus – ilgiausio *CA* sutrikimo įvykio (*LCAI*) trukmę ir *LCAI* dozę.

3. Akies arterijos kraujotakos ir *nICP* matavimo modeliavimas buvo atliktas Lietuvos energetikos institute *COMSOL Multiphysics software v5.1* programiniu paketu; *in vivo* validacija (1 val. trukmės nenutrūkstama stebėsena) buvo atlikta Respublikinės Vilniaus klinikinės ligoninės neurochirurginiame skyriuje; invazinis *ICP* buvo stebimas naudojant *Codman ICP* monitorių su kateterio tipo jutikliu ir *ICM+ v8.2* programine įranga; *nICP* buvo naudojant 2 gylių transkranijinį doplerį *Vittamed 205*, sukurtą STMI.

4. Galimos glaukomos rizikos šuntuojamiems NPH pacientams naratyvinė literatūros apžvalga buvo atliekama naudojantis *Pubmed* internetiniu resursu.

Rezultatų praktinė reikšmė

Disertacijoje nagrinėjami 4 tyrimų rezultatai prisideda prie HTG ir NTG diagnozės tikslinimo, suteikiant papildomą vertę – pasiūlant 2 naujus biožymenis *lowICP* ir *detCA*, kurie konkrečiam pacientui gali būti išmatuoti neinvaziniu būdu, naudojant mobilią ir santykinai nebrangią įrangą. Papildomų glaukomos biožymenų panaudojimas GL diagnostikoje atitinka populiarėjančios precizinės medicinos [14] tendenciją ir galėtų prisidėti prie glaukomos vystymosi pristabdymo ar net gydymo, realizuojant HTG ir NTG gydymo idėjas, paremtas minėtais BM, atitinkamai: LC

deformacijos normalizavimu neigiamu slėgiu, specialiai parinktais jogos pratimais (HTG atveju) bei sutrikusios *CA* normalizavimu, taikant PSO rekomenduojamas gyvensenos intervencijas, specialiai parinktus jogos pratimus (NTG atveju); taip pat galėtų prisidėti prie glaukomos rizikos suvaldymo NPH atveju.

Ginami teiginiai

1. Intrakranijio slėgio neinvazinių matavimų (*nICP*) tyrimo rezultatai parodė, kad tiek (ypač) aukšto akispūdžio glaukoma (HTG), tiek ir normalaus akispūdžio glaukoma (NTG) sergančių pacientų *nICP* vidurkio vertė yra žemesnė už normaliąją (HS) *nICP* vidurkio vertę; žemesnė už normaliąją *nICP* vertė *lowICP* signalizuoja apie anormalų slėgių skirtumą *IOP−ICP*, galintį sukelianti LC deformaciją ir glaukomos riziką, todėl gali būti vertinama kaip papildomas HTG ir NTG biožymuo, tuo suteikiant papildomą pridėtinę vertę glaukomos (ypač HTG) diagnostikai ir pasiūlant neinvazinio gydymo idėjas.

2. Smegenų kraujotakos autoreguliacijos neinvazinės stebėsenos (*nCA*) tyrimo rezultatai parodė, kad NTG pacientų *CA* yra sutrikusi, o HTG pacientų *CA* nėra sutrikusi; sutrikusios *CA* statusas (*detCA*) gali būti vertinamas kaip papildomas NTG biožymuo, tuo suteikiant papildomą pridėtinę vertę glaukomos (ypač NTG) diagnostikai ir pasiūlant neinvazinio gydymo idėjas.

3. Glaukomos rizikos, kylančios gydant normalaus slėgio smegenų vandenligę (NPH), tyrimų rezultatai sufleruoja, kad vietoj saugaus *ICP* viršutinio slenksčio būtina naudoti saugaus *nICP* intervalą ir rekomenduoti pacientams reguliarius *nICP* ir *nCA* matavimus bei reguliarią oftalmologinę apžiūrą, norint įvertinti ir suvaldyti glaukomos riziką.

Rezultatų pristatymas moksliniuose straipsniuose ir mokslinėse konferencijose

Tyrimų rezultatai buvo publikuoti 4 straipsniuose [9–12], Q1–Q2 lygio žurnaluose, priklausančiuose WoS tinklui, turinčiuose įtakos faktorių IF, ir pristatyti 4 tarptautinėse mokslinėse konferencijose.

Mokslinės literatūros apžvalga

Biožymenys

Biožymuo (BM) nusakomas kaip „apibrėžta savybė, kuri matuojama kaip normalių biologinių procesų, patogeninių procesų arba atsako į poveikį ar intervenciją rodiklis“ [15]. Diagnostinis BM (DBM) nustato arba patvirtina dominančios ligos ar būklės buvimą arba identifikuoja asmenį, sergantį tam tikra liga, taip pat DBM gali iš naujo apibrėžti ligos klasifikaciją [15].

BM – svarbi precizinės medicinos (angl. *Precision medicine*, PM) koncepcijos dalis. Dažniausiai vartojami PM apibrėžimai apima individualizuoto gydymo aspektą ir PM apibrėžia kaip „gydymą, nukreiptą į atskirų pacientų poreikius, remiantis genetinėmis, BM, fenotipinėmis ar psichosocialinėmis charakteristikomis, kurios išskiria konkretų pacientą iš kitų pacientų su panašia klinikine būkle“ [16]. Asmeninis požiūris į pacientą – esminis PM aspektas, o nauja biomedicininė informacija gali papildyti esminę informaciją, neapsiribojančią anksčiau stebėtais požymiais ir simptomais; šiuo požiūriu, PM reiškia šios koncepcijos naujumą, t. y. įvairių individualių duomenų, įskaitant naujus BM, įtraukimą [14].

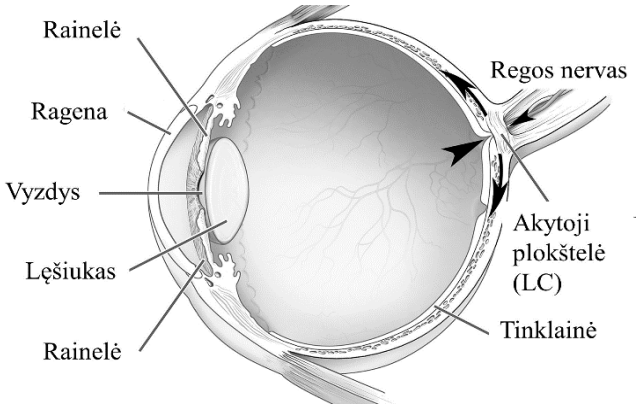
Glaukoma ir jos diagnostika

Žmogaus akis nuolat išskiria nedidelį kiekį skaidraus vandeningojo skysčio, kuris maitina akį ir palaiko jos pripildymą oru. Toks pat kiekis išteka per trabekulinę tinklainę akies srityje, vadinamą drenažo kampu [1]. Dėl šio proceso akispūdis (angl. *Intraocular pressure, IOP*) išlieka stabilus. Jei drenažo kampas veikia netinkamai, skystis kaupiasi. Akies viduje padidėja *IOP*, pažeidžiamas akies nervas, dėl to atsiranda regos lauko sutrikimų ir gali išsivystyti glaukoma [17]. Glaukoma – daugiaveiksnis progresuojantis neurodegeneracinis sutrikimas, kuriam būdingas akies nervo galvutės (ONH) pažeidimas, regos prastėjimas [18] arba visiškas praradimas. Įvairių šaltinių duomenimis, glaukomai priskiriama pirma [2] arba antra vieta [19] negrįžtamo regos praradimo priežasčių sąraše pasaulyje.

Pagal sukeliančias priežastis glaukoma skirstoma į pirminę ir antrinę (atsirandanti dėl kitų ligų ar jų gydymo poveikių). Pagal akies skysčio drenažo kampo anatomiją glaukoma gali būti atviro arba uždaro kampo [1]. Pirminė atviro kampo glaukoma (POAG) – labiausiai paplitęs glaukomos tipas pasaulyje. Ilgą laiką buvo manoma, kad didesnis už normalų *IOP* yra pagrindinis glaukomos rizikos BM, lemiantis jos išsivystymą. Tačiau tyrimai rodo, kad yra atvejų, kai *IOP* neperžengia normos [20, 21]. Pagal akispūdžio vertę POAG skirstoma [18, 22–24] į aukšto akispūdžio glaukomą (HTG) – kai padidėjęs *IOP* > 21 mmHg; ir normalaus akispūdžio glaukomą (NTG) – kai *IOP* neperžengia normos (*IOP* ≤ 21 mmHg).

Tyrimai rodo, kad, be jau naudojamo *IOP*, vienu iš galimų papildomų BM gali būti laikomas *ICP* [25, 26]. Kai kuriuose tyrimuose NTG pacientų *ICP* buvo gerokai mažesnis už HTG pacientų ar sveikų asmenų (HS) [21, 27–29]. Kituose tyrimuose nenustatyta reikšmingo *ICP* skirtumo tarp NTG ir HS grupių. Tai leidžia manyti, kad NTG atveju, be *IOP* ir *ICP*, egzistuoja daugiau įtakos veiksnių [30].

Galinėje skleros dalyje, giliai akies nervo galvutėje [31], yra sietą primenanti struktūra – akytoji plokštelė (lot. *Lamina cribrosa*, LC) (1.5–1.6 pav.), pro kurią tinklainės ganglinių ląstelių aksonai išeina iš akies [32, 33] prieš suformuodami ON [34]. Retrolaminarinė erdvė supa ON iš karto už LC [35]. LC skiria intraokulinę ir retrolaminarinę erdves, atlikdama barjero tarp *IOP* ir *ICP* vaidmenį [36] ir yra galima aksonų pažeidimo vieta (1.6 pav.).



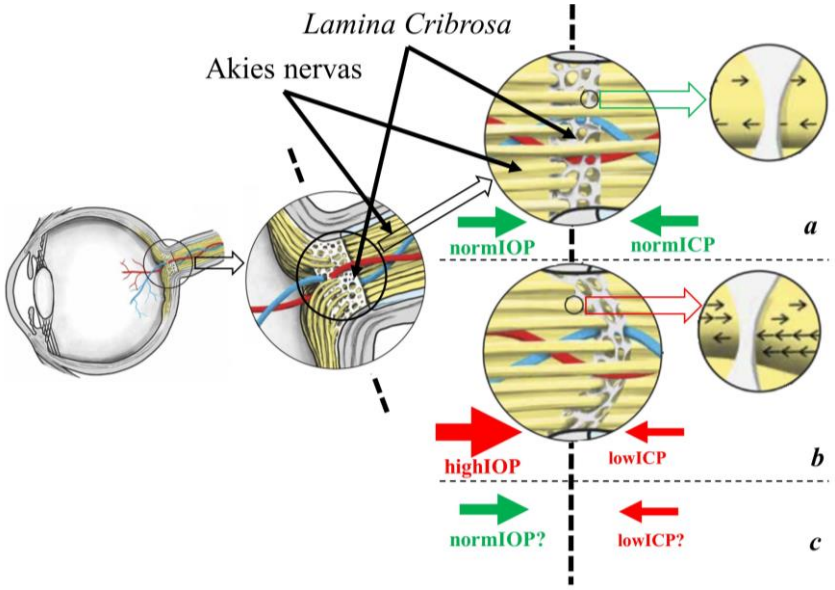
1.5 pav. Akytosios plokštelės (LC) vieta akies pjūvyje (adaptuota iš [37])

Egzistuoja kelios glaukomos priežasčių teorijos, iš jų išsiskiria, pvz., mechaninė ir kraujagyslių teorijų grupės [38–40]. Mechaninėje teorijoje glaukoma laikoma tiesiogine *IOP* padidėjimo pasekme, pažeidžiančia LC ir akies nervo (ON) galvutę [41, 42]. Kraujagyslių teorija teigia, kad glaukoma yra per mažo ON slėgio pasekmė [43, 44], o tą gali lemti kraujagyslių veiklos sutrikimai, tokie kaip spazmai, kraujagyslių ligos, autoreguliacijos sutrikimai [45, 46].

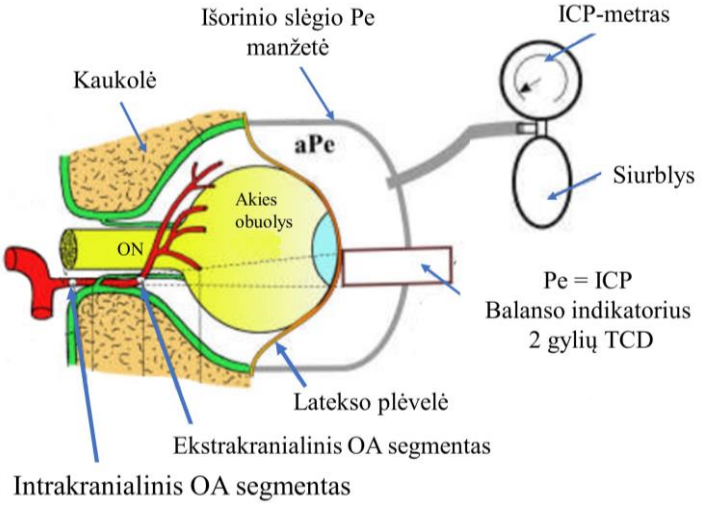
Slėgių, veikiančių LC, skirtumas vadinamas translaminariniu LC slėgio gradientu (angl. *Translaminar cribrosa pressure gradient*, *TCPG*) ir apskaičiuojamas: $TCPG = (IOP - ICP) / LC\ storis$. Buvo pasiūlyta idėja apie *TCPG* kaip pagrindinį veiksnį, lemiantį LC deformaciją ir aksonų pažeidimą [35, 48]. Remiantis šia hipoteze, padidėjus *IOP* arba sumažėjus *ICP*, *TCPG* padidėja, ir tai gali sukelti LC deformaciją bei ON pažeidimą [49]. NTG atveju *IOP* neperžengia normos, todėl priežastis gali būti *ICP* sumažėjimas arba kiti veiksniai, nesusiję su *IOP* ir *ICP*. 1.6 pav. schematiškai pavaizduota LC veikiančių slėgių *IOP* ir *ICP* vieta akies pjūvyje, *IOP* ir *ICP* verčių skirtumo kombinacijos, anormalaus *IOP−ICP* poveikio bei aksonų transporto pakitimai dėl LC deformacijos.

ICP matavimai yra apriboti dėl invazinio matavimo pobūdžio, tačiau šio apribojimo pavyko išvengti matuojant *ICP* neinvaziniu būdu (*nICP*). Metodas, pasižymintis kliniškai priimtinu tikslumu, preciziškumu ir diagnostiniu patikimumu, buvo sukurtas STMI [50, 51] ir gali būti taikomas platesnėms pacientų grupėms, ypač fiziologiškai sąmoningiems pacientams, tarp jų ir sergantiems glaukoma. Metodas pagrįstas natūralaus balanso principu (panašiu į kraujospūdžio matavimą), matuojant kraujo tėkmės greitį intrakranijiniame ir ekstrakranijiniame akies arterijos (OA)

segmentuose vienu metu (1.7 pav.), naudojant dviejų gylių transkranijinį doplerį (TCD) [52, 53]. Aukščiau minėtos *TCPG* įtakos hipotezės patvirtinimo naudai byloja tyrimų rezultatai, kurių metu nustatyta *ICP* vertė, mažesnė už normalią [54–57].



1.6 pav. LC veikiantys slėgiai *IOP* ir *ICP*, jų verčių skirtumo variantai ir pasekmės. *a* – HS atvejis; *b* – HTG atvejis; *c* – NTG ir NPH atvejai (adaptuota iš [85])



1.7 pav. *nICP* matuoklio, pagrįsto 2 gylių TCD (ir slėgių balanso principu), struktūrinė schema (adaptuota iš [58])

Siekiant išsiaiškinti GL įtaką pacientų *ICP*, buvo atliktas *nICP* matavimo glaukomos pacientams tyrimas [9].

ICP ir *IOP* yra veikiami cirkadinių svyravimų, todėl momentiniai šių slėgių matavimai tam tikru metu gali suteikti nepakankamai diagnostinės informacijos [27, 59]. *ICP* ir *IOP* stebėsena reikalinga norint tiksliau diagnozuoti NTG ir HTG tais atvejais, kai *ICP* vertės yra mažesnės už normalias. Papildomame tyrime [11], siekiant ištirti galimybę naudoti OA kaip *nICP* jutiklį stebėsenai, buvo taikomas skaitmeninis modeliavimas. Po to buvo atliktas bandomasis *in vivo* klinikinis tyrimas – lygiagreti invazinio *ICP* ir neinvazinio *ICP* stebėsena, siekiant ištirti OA kaip *ICP* jutiklio teisiškumą, tikslumą bei panaudojimą *nICP* ilgalaikei stebėsenai.

Grįžtant prie NTG, jos kilmės paaiškinimai tebėra prieštaringi. Tyrimų [60, 61] duomenimis, glaukomos priežastis yra akies kraujotakos autoreguliacijos disfunkcija. Kiti tyrimai rodo, kad sutrikusi akių kraujotaka yra pagrindinis veiksnys, susijęs su NTG patogeneze [62].

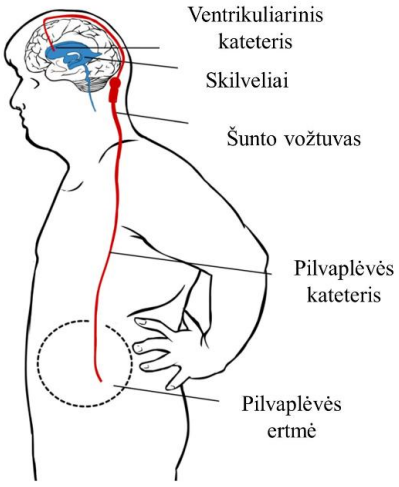
Glaukomos atveju kraujagyslių kraujotakos sutrikimai gali būti vienas iš *CA* sutrikimo rezultatų ir galėtų paaiškinti GL ryšį su tokiais sutrikimais, kaip kraujagyslių spazmas, endotelio disfunkcija, migrena [63]. Akyje palaikoma stabili kraujotaka, tačiau tik iki tam tikrų ribų, ji yra smegenų kraujotakos atspindys [64–66]. Smegenų kraujagyslių sistema reaguoja į arterinio kraujospūdžio (*ABP*) arba smegenų perfuzinio slėgio (*CPP*) pokyčius, palaikydama stabilią smegenų kraujotaką. Galvos smegenų *CPP* stabilizavimo, nepaisant smegenų kraujotakos svyravimų, mechanizmas vadinamas smegenų kraujotakos autoreguliacija (*CA*). Akių kraujotakos autoreguliacijos panašumas į *CA* pasiūlė hipotezę, kad akių kraujotakos sutrikimas yra susijęs su *CA* sutrikimu glaukomos atveju ir ypač jei tai yra NTG. Tyrimų studija [10] skirta šios hipotezei, taip pat ir darbinės hipotezės b) daliai patikrinti.

Įprastiniai *CA* matavimo metodai turi apribojimų dėl invazinio pobūdžio (pvz., kateterizacija, arterinė punkcija). Šiems apribojimams įveikti buvo pasiūlyti keli neinvaziniai *CA* stebėsenos metodai. Vienas iš metodų, sukurtas STMI, panaudotas glaukomos pacientų *nCA* stebėsenos tyrimo metu [10]. Studijoje naudojamas ankstesniuose tyrimuose išbandytas metodas, pagrįstas tūrinio reaktyvumo indekso (VR_x) skaičiavimu. Jo privalumas – galimybė išsamiau įvertinti *CA*, nes intrakranijinio kraujo tūrio (*IBV*) pokyčiai vertinami, matuojant ultragarsinio signalo sklidimo laiką abiejuose smegenų pusrutuliuose [67].

Smegenų vandenligė

Papildoma tyrimų idėja, kryptis ir pagrindas studijai, atsiradę matuojant glaukomos pacientų *nICP* – normalaus slėgio smegenų vandenligės (NPH) pacientų gydymo metu kylanti glaukomos rizika. NPH yra būdinga suaugusiems ir geriatriniams pacientams pavojinga gyvybei neurologinė liga, kurios simptomai – išsiplėtę smegenų skilveliai, klinikiniai eisenos sutrikimai, šlapimo nelaikymas, kognityvinių funkcijų pablogėjimas [68–70]. Simptomus lemia smegenų skysčio (*CSF*) transportavimo iš gamybos vietų į absorbcijos vietas sutrikimas [71]. *ICP* didžiąją laiko dalį išlieka normalus [72], iš čia ligos pavadinimas. Populiariausias

NPH gydymo būdas – skilvelinis šuntavimas, nuleidžiantis *CSF* perteklių į pilvaplėvės ertmę (1.8 pav.) [73].



1.8 pav. Skilvelinis šuntas (adaptuota iš [74])

Idėja, kad NPH gydymas gali sukelti NTG [75, 76], paskatino atlikti papildomą tyrimą [12], patikrinant darbinės hipotezės c) dalį.

2. PATEIKIAMŲ STRAIPSNIŲ APŽVALGA

Bendras įvadas

Keturių straipsnių santrauka atspindi 4 tyrimų rezultatus, siekiant juos interpretuoti ir iš holistinių pozicijų išanalizuoti papildomų biožymenų įtraukimo galimybes, pridedant vertės glaukomos diagnostikai ir suformuluojant galimo gydymo idėjas. Pagrindiniai tyrimai:

1. HTG ir NTG sergančių pacientų ir HS grupių *nICP* matavimas bei grupių rezultatų palyginimas, siekiant patikrinti darbinės hipotezės a) dalį;
2. HTG ir NTG pacientų ir HS grupių *nCA* stebėsena bei grupių rezultatų palyginimas, siekiant patikrinti darbinės hipotezės b) dalį;

Papildomi tyrimai:

3. *nICP* ilgalaikės stebėsenos galimybių tyrimai;
4. NTG rizikos, kylančios dėl NPH gydymo metu mažėjančio *ICP*, tyrimai, siekiant patikrinti darbinės hipotezės c) dalį.

2.1. Atviro kampo glaukoma sergančių pacientų ir sveikų asmenų neinvazinių intrakranijinio slėgio matavimų perspektyvinis klinikinis tyrimas

Publikacijos originalus pavadinimas: „Prospective Clinical Study of Non–Invasive Intracranial Pressure Measurements in Open–Angle Glaucoma Patients and Healthy Subjects“ [9].

Šio tyrimo tikslas buvo įvertinti *nICP* skirtumus tarp glaukoma sergančių pacientų (HTG ir NTG) ir sveikų tiriamųjų (HS). Santraukoje aptarti esminiai aspektai, susiję su darbine hipoteze. Autoriaus indėlis: pirminio projekto teksto rengimas, įskaitant rezultatų ir literatūros analizę, diskutuojant su bendraautoriais; papildomos išvados ir naujų biožymenų rekomendacijos bei HTG gydymo idėjos, žvelgiant iš holistinio atskaitos taško.

Metodai

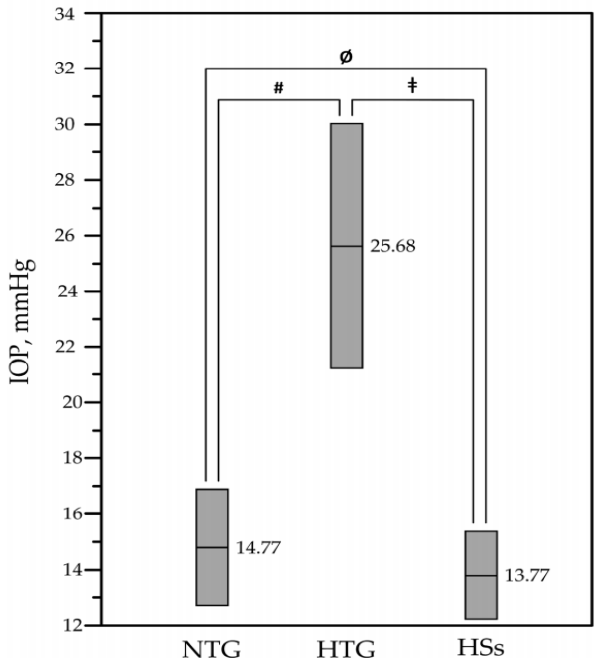
Tyrimas atliktas LSMU ALK, jame dalyvavo glaukomos pacientai (HTG bei NTG) ir sveiki asmenys (HS). Glaukomos grupės buvo sudarytos vadovaujantis įtraukimo kriterijais, tokiais kaip GL diagnozė ir kt. HS atveju į tyrimą buvo įtraukti savanoriai, kurie anksčiau nesirgo glaukoma ar kitomis ligomis, galinčiomis iškreipti rezultatus. *nICP* matuoti buvo naudojama tik viena akis, pasirinkta atsitiktiniu būdu. Prieš *nICP* matavimo sesiją Goldmano aplanaciniu tonometru buvo išmatuotas *IOP*. Visi tyrimai buvo atliekami dienos metu nuo 8 iki 14 val. *nICP* buvo matuojamas *Vitamed 205* matuokliu, kuriam nereikia kalibravimo. Jo veikimas pagrįstas dviejų gylių TCD, vienu metu matuojančiu kraujo greitį intrakranijiniame (IOA) ir ekstrakranijiniame (EOA) OA segmentuose [50]. 2 MHz ultragarso keitiklis kartu su

oro pripildyta slėgio manžete įmontuotas į rėmą, tvirtinamą ant galvos. Išorinis slėgis *Pe* per slėgio manžetę perduodamas EO. Taigi IOA yra veikiamas *ICP*, o EOA veikiamas *Pe*. Kraujo srauto greitis abiejuose OA segmentuose yra maždaug vienodas, kai *Pe = ICP*, vadinasi, šių slėgių sutapimo momentu *ICP* vertė matoma *Pe* matavimo skalėje. *Pe* buvo didinamas nuo 0 iki 20 mmHg kas 4 mmHg, iki kraujo greičių IOA ir EOA sutapimo momento; matavimų sesija truko iki 10 min., tiriamieji buvo gulimoje padėtyje [9].

Statistinė analizė atlikta naudojant *IBM SPSS Statistics v.23.0* programinę įrangą. Buvo apskaičiuota *nICP* vidutinė reikšmė (angl. *Mean*) ir standartinis nuokrypis (angl. *Standard deviation*, *SD*), atliktas visų grupių Kolmogorovo ir Smirnovo skirstinio normalumo testas, vienpusis ANOVA testas ir Tukey daugkartinio palyginimo testas.

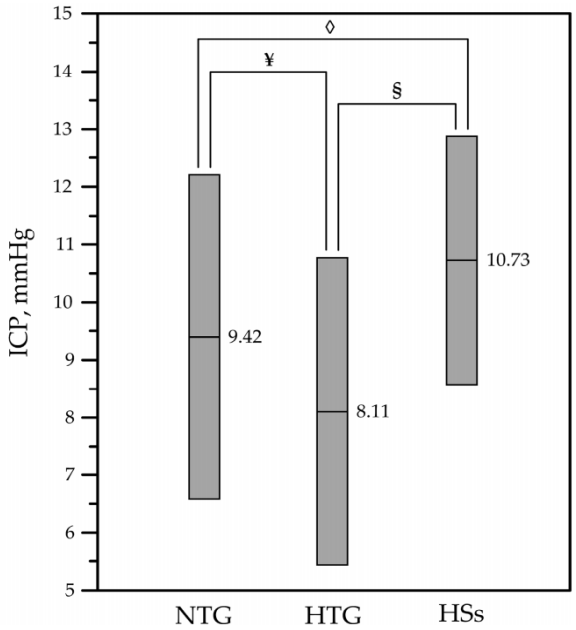
Rezultatai

Į statistinę analizę įtraukti 217 tiriamųjų (95 NTG, 60 HTG, 62 HS) duomenys. NTG pacientų *IOP* buvo statistiškai reikšmingai ($p < 0,05$) mažesnis, palyginti su HTG pacientais, HS pacientų *IOP* buvo statistiškai reikšmingai ($p < 0,05$) mažesnis, palyginti su HTG (2.1.1 pav.).



2.1.1 pav. Tiriamųjų grupių vidutinės *IOP* vertės su standartiniu nuokrypiu.
Ø – skirtumas statistiškai reikšmingas ($p < 0,05$) lyginant NTG ir HS grupių *IOP* vidurkius;
– skirtumas statistiškai reikšmingas ($p < 0,05$) lyginant NTG ir HTG;
≠ – skirtumas statistiškai reikšmingas ($p < 0,05$), lyginant HTG ir HS.

Tukey testu (0,05 reikšmingumo lygmuo) nustatyti tokie grupių vidutinio *nICP* palyginimo rezultatai: $nICP_{NTG}$ vertė (9,42 ± 2,83 mmHg) buvo statistiškai reikšmingai (p = 0,007) žemesnė už $nICP_{HS}$ (10,73 ± 2,16 mmHg). $nICP_{HTG}$ vertė (8,11 ± 2,68 mmHg) buvo reikšmingai (p = 0,008) žemesnė už $nICP_{NTG}$ (9,42 ± 2,83 mmHg) ir reikšmingai (p < 0,001) žemesnė už $nICP_{HS}$ (10,73 ± 2,16 mmHg). Rezultatai pateikti 2.1.2 paveiksle ir 2.1.1 bei 2.1.2 lentelėse.



2.1.2 pav. Tiriamųjų grupių vidutinės *nICP* vertės su standartiniu nuokrypiu.
◊ – skirtumas statistiškai reikšmingas (p = 0,007), lyginant NTG ir HS grupių vidurkius;
¥ – skirtumas statistiškai reikšmingas (p = 0,008) lyginant NTG ir HTG;
§ – skirtumas yra statistiškai reikšmingas (p < 0,001) lyginant HTG ir HS

2.1.1 lentelė. Tiriamųjų grupių *nICP* vidurkis

Grupė	**N**	***nICP***
HTG	60	8,11 ± 2,68
NTG	95	9,42 ± 2,83
HS	62	10,73 ± 2,16

2.1.2 lentelė. Grupių *nICP* vidurkio reikšmių palyginimas.
Tukey testo rezultatai esant 0,05 reikšmingumo slenksčiui

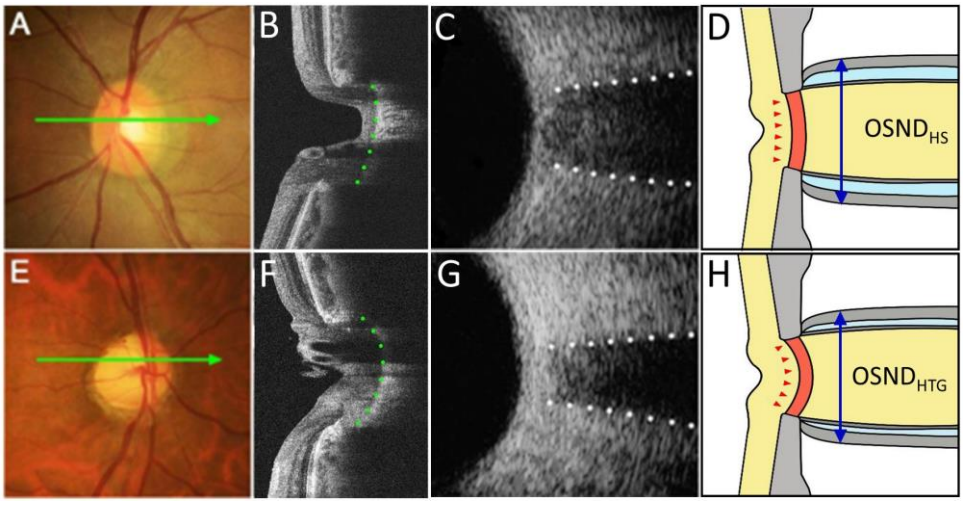
Grupės	***p***	***nICP* skirtumas**
NTG vs HS	0,007	reikšmingas
HTG vs NTG	0,008	reikšmingas
HTG vs HS	**0,001**	reikšmingas

Rezultatų interpretacija

Žemesnio už normalų *ICP* vaidmuo akies nervo glaukomos neuropatijos patogenezėje buvo aprašytas XX a. septintojo dešimtmečio pabaigoje, tačiau pagrindinis mechanizmas vis dar sunkiai suprantamas; buvo atlikta keletas tyrimų su gyvūnais, siekiant išsiaiškinti ryšį tarp smegenų skysčio (angl. *cerebrospinal fluid*, CSF) slėgio ir glaukomos [9]. Ribotame skaičiuje klinikinių tyrimų nustatyta, kad NTG atvejais CSF slėgis mažesnis, palyginti su HS atvejais [28, 77]. Tyrimų skaičių riboja invazinis CSF slėgio matavimo pobūdis. Standartinės klinikinės *ICP* matavimo procedūros – invazinės: stuburo (juosmens srityje) punkcijos metodas [77, 78] arba keitiklio įvedimas į kaukolės vidų. Šiame tyrime *nICP* matuotas arčiau LC, ir šis metodas leidžia atskirti slėgį tiek intrakranijinėje, tiek akies nervo subarachnoidinėje erdvėje.

Šiame tyrime HTG pacientų vidutinis *nICP* buvo statistiškai reikšmingai mažesnis nei NTG pacientų ir HS, o NTG pacientų vidutinis *ICP* buvo reikšmingai mažesnis nei HS. NTG grupės *nICP* vidurkio reikšmė panaši į ankstesnių tyrimų rezultatus [78]. HTG ir HS *nICP* vidutinės vertės panašios į kito ankstesnio tyrimo rezultatus, o NTG vidutinė *nICP* vertė skyrėsi [79]. Pagrindinė NTG priežastis išliko neaiški.

2023 m. publikuoto Seung HL et al. tyrimo [13] optinės koherentinės tomografijos (OCT) ir ultragarso vaizdai patvirtina mūsų rezultatus. 2.1.3 pav. HS ir NTG paciento akių palyginimas iliustruoja neigiamą koreliaciją tarp LC kreivumo indekso (*LCCI*) ir akies nervo apvalkalo skersmens (*ONSD*); (A–D) HS akis: LC palyginti plokščia, *ONSD* platus; (E–H) NTG akis: LC išlenkta *ONSD* siauras. A, E – stereoskopinės OND nuotraukos; B, F – Cirrus HD OCT B–scan vaizdai, gauti ties atitinkamomis plokštumomis (žalios rodyklės A, E). C, G – transorbitinio ultragarso vaizdai D, H – akies nervo schema. $LCCI_{HTG} > LCCI_{HS}$, $ONSD_{HTG} < ONSD_{HS}$.



2.1.3 pav. Ryšys tarp *LCCI* ir *ONSD* HS ir NTG atvejais. (adaptuota iš [13])

HTG neinvazinio gydymo idėjos ir perspektyvos

HTG šiuo metu gydoma *IOP* mažinimo metodu – medikamentiniais ir chirurginiais būdais, tačiau medikamentai tik pristabdo ligos eigą, o invazinės procedūros vis dar rizikingos [81]. Čia ypač išsiskiria amerikiečių oftalmologo MD Johno Berdahlio ir kolegų idėjos ir tyrimai, 2018–2021 m. publikacijos rodo HTG naują galimo neinvazinio glaukomos gydymo tendenciją taikant akių fizioterapijos procedūras, pagrįstas slėgine mankšta [80–87]. Žemiau apžvelgiami straipsniai, kurie yra artimiausi disertacijos tikslams ir uždaviniams, norint pademonstruoti neinvazinio glaukomos gydymo perspektyvas.

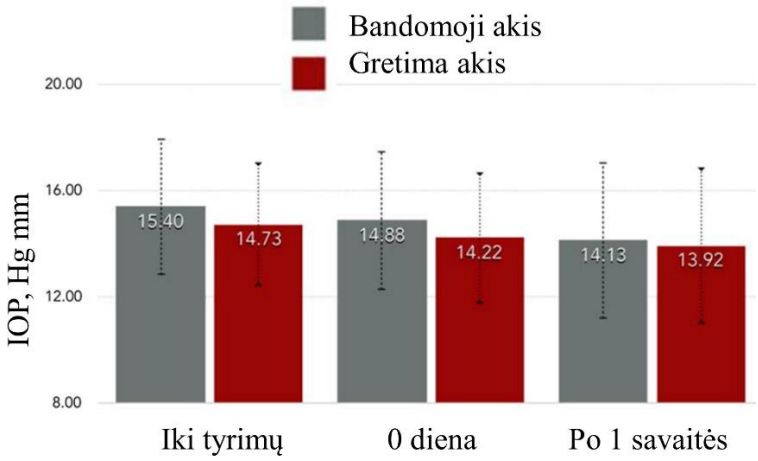
Pačiam pirmam sveikų savanorių tyrimui buvo sukurtas ir naudojamas portatyvus slėgio reguliatorius (angl. *multi–pressure dial*, MPD), kurį sudaro siurblys, žarnele sujungtas su neigiamo slėgio (vakuuminiais) „plaukiko“ akiniais, apgaubiančiais akis (2.1.4 pav.).

2.1.4 pav. Slėgio reguliatorius MPD (adaptuota iš [80])

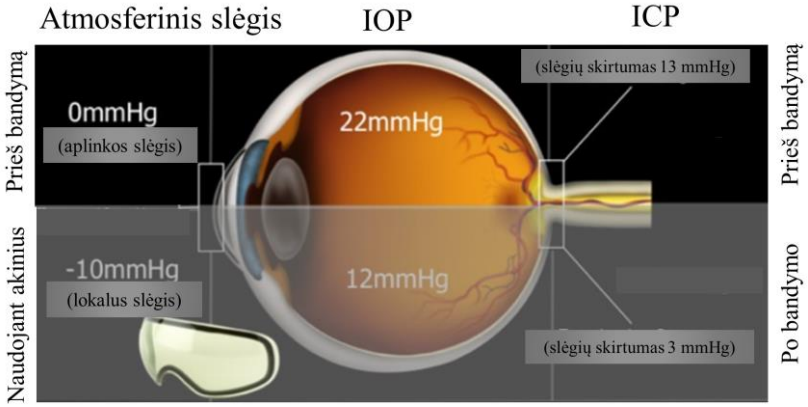
Reguliatoriaus oro siurblys sukelia neigiamą slėgį akių zonoje, dėl to akispūdis sumažėja (2.1.5–2.1.6 pav.). Pilotinio 30 sveikų tiriamųjų tyrimo metu buvo tiriama dešinioji akis, kairioji buvo kontrolinė. Rezultatai [80] rodo *IOP* sumažėjimą abiejose akyse jau pirmą („nulinę“) dieną.

Visų parametrų, įskaitant, *IOP*, matavimai buvo atlikti prieš uždedant MPD ir buvo pakartoti iš karto jį nuėmus. Sureguliavus MPD, tiriamajai akiai palaipsniui buvo didinamas neigiamas slėgis iki −15 mmHg vertės, kuri buvo išlaikyta 30 min., po to lėtai mažinama iki pradinės. Nuėmus prietaisą (0 diena), iš karto buvo pakartoti

pradiniai matavimai. Savaitės (6–8 d.) laikotarpiu tiriamieji grįžo pakartoti tyrimų. Praėjus 1 savaitei po tyrimo tiek tiriamųjų, tiek kontrolinės grupės akių *IOP* (2.1.5 – 2.1.6 pav.) sumažėjo statistiškai reikšmingai, tačiau klinikinė reikšmė dar nenustatyta. Nepageidaujamų poveikių nepastebėta, dalyviai gerai toleravo MPD. Pagrindiniai saugos parametrai po trumpalaikio poveikio išliko stabilūs. Palankūs šio tyrimo saugos rezultatai patvirtina MPD saugos profilį ir skatina toliau tirti šį prietaisą ir metodą kaip galimą glaukomos neinvazinį gydymo būdą.



2.1.5 pav. MPD tyrimo *IOP* vidurkis ± *SD* (adaptuota iš [80])



2.1.6 pav. Tyrimo metu naudojami slėgiai. Lokaliai sumažinus slėgį prieš akį, sumažėja *IOP* ir atkuriamas normalus *IOP*−*ICP*, normalizuojantis akies nervo funkcijas (adaptuota iš [80])

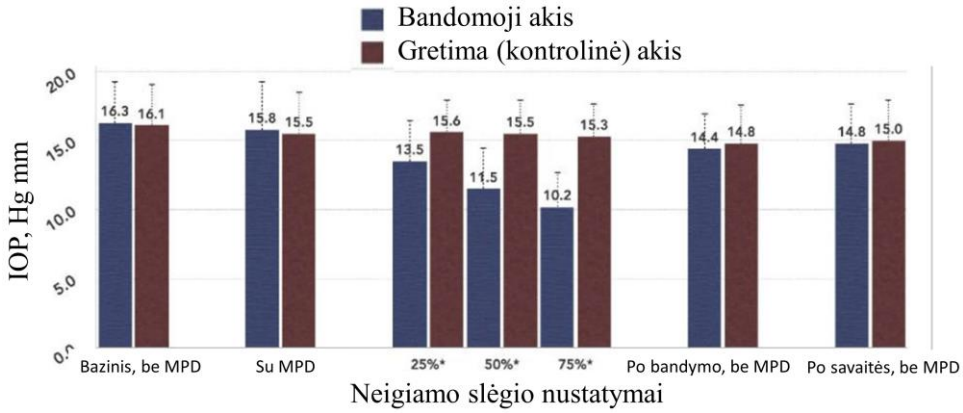
Kitas saugumo tyrimas vyko jau dalyvaujant 10 POAG pacientų, taikant neigiamą slėgį −10 mmHg vienoje akyje 8 val. ir aplinkos atmosferos slėgį kontrolinėje akyje [81]. Statistiškai reikšmingų *IOP* pokyčių iš karto po 8 val. trukmės

tyrimo laikotarpio ir po 1 savaitės nebuvo nustatyta. Tiriamieji teigiamai vertino MPD kaip glaukomos gydymo būdą. MPD pasižymėjo saugumu, o matuojami parametrai išliko stabilūs po 8 val. dėvėjimo su neigiamu slėgiu, dalyviai neigiamą slėgį toleravo sėkmingai. Neigiamo slėgio taikymas nepertraukiamai 8 val. pasirodė saugus.

Toliau buvo atliekami neigiamo periokulinio slėgio poveikio *IOP* modeliavimo tyrimai [82] ir 10 POAG pacientų 7 paras naktį dėvimo MPD saugumo vertinimas [83], kurio metu atsitiktiniu būdu parinktai akiai buvo taikytas −10 mmHg slėgis. Nustatyta, kad *IOP* sumažėjo > 20 % papildomai prie taikomo gydymo, kas yra kliniškai ir statistiškai reikšminga. MPD pasirodė kaip saugus dėvėti naktį, miegant, ir pasirodė kaip galimas naujas naktinės *IOP* kontrolės glaukomos gydymo būdas, ypač darant prielaidą, kad pacientai galėtų prietaisą nešioti ilgiau nei 7 dienas. Tyrime buvo naudoti modifikuoti MPD modeliai (2.1.7 pav.)

2.1.7 pav. MPD modelis ir jo modifikuota versija. Akinių lęšiuose yra prieiga, leidžianti atlikti pneumatonometrinius matavimus neigiamo slėgio metu (adaptuota iš [83])

Dar vienas tyrimas – daugiaslėgio MPD *IOP* mažinančio poveikio vertinimas esant skirtingiems neigiamo slėgio nustatymams, dalyvaujant 65 sveikų tiriamųjų [84] Atsitiktinės atrankos būdu buvo parinkta 60 min. netaikyti neigiamo slėgio arba 20 minučių taikyti 25%, 50% ir 75% bazinio *IOP* neigiamą slėgį. Pagrindinis rezultatų rodiklis buvo vidutinis *IOP*, kai buvo taikomas neigiamas slėgis. Rezultatai parodė, kad tiriamųjų ir kontrolinių akių vidutinių *IOP* vertės skyrėsi statistiškai reikšmingai ($p < 0{,}001$) visų neigiamo slėgio verčių atvejais, lyginant su pradine verte (2.1.8 pav.). Neigiamas slėgis į periokulinę erdvę naudojant daugiaslėgio MPD gali sukelti *IOP* sumažėjimą, kai prietaisas dėvimas aktyvavus neigiamą slėgį. Tyrimo autorių žiniomis, ši technologija yra pirmasis nefarmakologinis, nelazerinis, nechirurginis *IOP* mažinimo metodas [84].



2.1.8 pav. Vidutinio *IOP* palyginimas tiriamojoje ir kontrolinėje akyje. Pradinė vertė (kairėje) rodo *IOP* matavimus, gautus prieš dėvint MPD. *NP* = neigiamas slėgis; MPD OFF – tiriamasis nedėvėjo prietaiso. * Skirtumas tarp tiriamosios ir kontrolinės akies šiais laiko momentais (25 %, 50 %, 75 %) statistiškai reikšmingai skyrėsi ($p < 0{,}001$) nuo *IOP* skirtumo tarp tiriamosios ir kontrolinės akies prieš neigiamo slėgio taikymą (adaptuota iš [84])

Tolesniame tyrime iškeliama hipotezė, kad periodiškas translaminarinio slėgio gradiento (*TLPG*) normalizavimas apsaugo nuo glaukomos pažeidimų, ir teoriniu lygmeniu aptariama, lyginant su kitų mokslininkų darbais bei glaukomos gydymo tendencijomis. Autoriai priėjo prie išvadų, kad gausėja įrodymų, jog *TLPG* yra pagrindinis glaukomos vystymosi veiksnys ir kad reikia naujų eksperimentinių ir klinikinių tyrimų, siekiant ištirti, ar periodinis *TLPG* normalizavimas apsaugo tinklainės ganglines ląsteles (angl. *Retinal ganglion cells*, RGC) [85]. Reikėtų tirti *TLPG* normalizavimo trukmę ir dažnumą, reikalingą siekiant išvengti RGC praradimo. Autoriai daro prielaidą, kad yra *IOP* padidėjimo trukmės ir dydžio riba, kurią peržengus nebegalima pasiekti RGC normalizavimo. Jei pavyks pagrįsti pateiktą teoriją, bus galima rinktis mažiau invazinius, trumpai veikiančius glaukomos gydymo būdus.

Kitas galimai potencialiai veiksmingas *IOP* mažinimo būdas – pritaikant kai kuriuos jogos metodus. Pastarosiomis dekadomis daugėja tyrimų, įrodymų ir straipsnių apie jogos įtaką sveikatai. Raktinio žodžio *yoga* paieškos Pubmed e–resurse rezultatai rodo, kad pirmieji moksliniai tyrimai datuojami 1948 m., tačiau nuo 2000–ųjų metų publikacijų daugėjo eksponentiškai [117]. Tyrimų, kuriuose buvo matuojama jogos įtaka GL pacientų *IOP*, rezultatai sufleruoja, kad joga gali tiek padidinti tiek ir sumažinti *IOP*, priklausomai nuo parinktų jos pratimų pobūdžio. Jasien et al. pilotinio tyrimo rezultatai parodė, kad jogos pratimai galva žemyn sukelia statistiškai reikšmingą ir greitą *IOP* padidėjimą netrukus po pratimų pradžios ir sumažėjimą netrukus po pratimų atlikimo sustabdymo [118]. Kitas tyrimas pademonstravo, kad joga ir meditacija sukėlė nuolatinį su *IOP* susijusio profilio sumažėjimą, tačiau nė vienas iš susijusių pokyčių nebuvo statistiškai reikšmingas [119]. Dada et al. studijoje teigiama, kad ankstesniuose GL pacientų tyrimuose

įrodyta, jog meditacija mažina *IOP*, streso biožymenis, gerina smegenų aprūpinimą deguonimi, gyvenimo kokybę ir kad tai pirmasis tyrimas, parodęs, kad sąmoningumu paremti streso mažinimo būdai (angl. *Mindfulness based stress reduction*, MBSR) gali pagerinti akies nervo perfuziją, matuojamą optinės koherentinės tomografijos – angiografijos metodu. MBSR galima rekomenduoti kaip GL gydymą, papildantį medikamentinį, siekiant padidinti ON galvutės perfuziją ir sumažinti *IOP*, o tai gali mažinti glaukomos progresavimą [120]. Kulkarni et al. nustatė, kad tam tikros pranajamos technikos (kvėpavimas dešine ir kaire nosies šnerve, kvėpavimas pakaitinėmis šnervėmis) buvo saugios ir neturėjo neigiamo poveikio didinant *IOP* sveikiems tiriamiesiems ir taip pat gali turėti teigiamą poveikį mažinant *IOP* [121].

Poskyrio išvados

1. Glaukomos pacientų *nICP* ($nICP_{GL}$) vidurkio vertė yra žemesnė už $nICP_{HS}$.

2. Žemesnė už normaliąją *ICP* (*lowICP*) vertė, išmatuota neinvaziškai ties LC, gali būti vertinama kaip glaukomos biožymuo, darantis įtaką akies nervo degeneracijai, tuo suteikiant papildomą pridėtinę vertę GL diagnostikoje, su klaidos tikimybe ≤ 5%.

3. *nICP* vidurkių skirtumas tarp bet kurių 2 dalyvių grupių yra statistiškai reikšmingas.

4. $nICP_{HTG} < nICP_{NTG} < nICP_{HS}$ lyginant visas 3 grupes.

5. Lyginant *nICP* vidurkį tik tarp glaukomos pacientų grupių: $nICP_{HTG} < nICP_{NTG}$; o NTG ir HS grupių palyginimo Tukey testo rezultatas ($p = 0{,}007$), nors ir patenka į reikšmingumo intervalą, skiriasi nuo HTG ir HS grupių palyginimo rezultato ($p = 0{,}001$) net 7 kartus; o nuo HTG ir NTG grupių palyginimo rezultato ($p = 0{,}008$) tik 1,14 karto, ir tai leidžia daryti prielaidą, kad:

   5.1. HTG atveju būtent padidėjęs *IOP*, kartu su sumažėjusiu *ICP*, sudaro slėgių skirtumą *IOP*−*ICP*, kuris deformuoja LC, sukeldamas glaukominius pakitimus;

   5.2. NTG atveju *IOP* yra normalus, bet glaukoma vystosi; $nICP_{NTG}$, nors ir žemesnis už $nICP_{HS}$ bei statistiškai reikšmingai skiriasi nuo $nICP_{HS}$ ir nuo $nICP_{HTG}$, akivaizdžiai skiriasi nuo $nICP_{HTG}$ santykinai nedaug, palyginti su skirtumu tarp $nICP_{HTG}$ ir $nICP_{HS}$. Vadinasi, NTG atveju, be *ICP*, galimai egzistuoja kitokie papildomi veiksniai, kuriuos išsiaiškinus, jie galėtų tapti NTG biožymenimis; kandidatas į tokius veiksnius – galimas *CA* sutrikimo statusas (*detCA*); tai suponuoja darbinės hipotezės b) dalies tikrinimą.

6. Turint galimybę neinvaziškai matuoti glaukomos pacientų *IOP* ir *ICP* (ir kartu netiesiogiai matuoti *IOP–ICP* ir jo poveikį LC), atsiveria HTG neinvazinio gydymo perspektyva, taikant fizioterapines slėgio mankštos procedūras bei tikslingai parinktus jogos pratimus. Reikalingi šių *IOP* mažinimo būdų (tiek atskirai, tiek ir juos sujungiant) įtakos *IOP* ir *ICP* (taip pat ir *IOP*−*ICP*) normalizavimui, LC formos normalizavimui po deformacijos tyrimai.

2.2. Atviro kampo glaukoma sergančių pacientų ir sveikų asmenų neinvazinės smegenų kraujotakos autoreguliacijos stebėsenos perspektyvinis bandomasis klinikinis tyrimas

Originalus straipsnio pavadinimas: „Prospective Pilot Clinical Study of Noninvasive Cerebrovascular Autoregulation Monitoring in Open–Angle Glaucoma Patients and Healthy Subjects“ [10].

Šiame tyrime pirmą kartą pritaikyti neinvaziniai ultragarso metodai, siekiant ištirti trijų grupių – NTG ir HTG pacientų bei sveikų asmenų (HS) *CA* dinamiką ir palyginti visų grupių rezultatus tarpusavyje. Autoriaus indėlis – duomenų analizė, teksto pirmos versijos pilnas parašymas, diskutuojant su kitais bendraautoriais; papildyta rezultatų interpretacija, 2 bandymai teikti publikuoti į nemokamus WoS žurnalus; papildomos išvados ir naujų biožymenų siūlymai bei NTG gydymo idėjos, žvelgiant iš holistinio atskaitos taško, paremto PSO rekomendacijomis.

Metodai

Šis klinikinis tyrimas atliktas LSMU ALK. Tyrime dalyvavo HTG ir NTG pacientai bei sveiki asmenys. HTG ir NTG grupės buvo suformuotos ALK, vadovaujantis įtraukimo į tyrimą kriterijais: oftalmologo patvirtinta klinikinė glaukomos diagnozė ir kt., pokyčiai akies nervo galvutėje ir regos lauko praradimas, atitinkantis glaukomą. Sveikų savanorių grupė buvo sudaroma iš savanorių, nesirgusių glaukoma ar kitomis ligomis, galinčiomis iškreipti tyrimo rezultatus.

Visų 3 grupių dalyvių *nCA* būklė buvo stebima naudojant inovatyvų neinvazinį ultragarsinį metodą, pagrįstą ultragarsinio signalo sklidimo tarp smilkinių laiko (angl. *Time of flight*, *TOF*) matavimo principu. *TOF* būdu galima įvertinti intrakranijinio tankio pokyčius akustiniame kelyje. Savo ruožtu pokyčiai susidaro dėl intrakranijinio kraujo tūrio (angl. *Intracranial blood volume*, *IBV*) svyravimų, kurie naudojami kaip intrakranijinio slėgio (arba smegenų kraujotakos) lėtųjų bangų pakaitalas vertinant *CA* [88–91].

TOF svyravimas atvirkščiai proporcingas *IBV* pokyčiams, nes ultragarso greitis kraujyje yra didesnis nei kituose intrakranijiniuose komponentuose (pvz., parenchimoje ir smegenų skystyje). Padidėjus kraujo kiekiui akustiniame kelyje, padidėja vidutinis santykinis ultragarso greitis ir sumažėja *TOF*: $\Delta IBV(t) \sim 1/TOF(t) \sim -\Delta TOF(t)$. Darant prielaidą, kad lėti *IBV* pokyčiai yra susiję su lėtais *ICP* pokyčiais (arba lėtais smegenų kraujotakos pokyčiais), tūriniam reaktyvumo indeksui *VRx* apskaičiuoti naudojome atvirkštinius $\Delta TOF(t)$ duomenis:

$$VRx = r\,[ABPsw(t);\, IBVsw] = r\,[ABPsw(t);\, -\Delta TOF(t)]\ [10, 92, 93], \qquad (1)$$

čia: $ABPsw(t)$ – arterinio kraujospūdžio lėtosios bangos, $IBVsw(t)$ – intrakranijinio kraujo tūrio lėtosios bangos, $\Delta TOF(t)$ – lėti TOF pokyčiai, atvirkščiai atspindintys lėtus IBV pokyčius $\Delta IBV(t)$; r – koreliacijos koeficientas.

Signalo nuskaitymo įrangą (*Vittamed 505* monitorius; *Boston Neurosciences*) sudaro galvos rėmas su 2 ultragarso keitikliais (2 MHz), išdėstytais priešingose galvos pusėse ties smilkinio kaulu. Ultragarso impulsas, perduodamas iš vieno keitiklio, sklinda per smegenų parenchimą ir smegenų skilvelius ir priimamas kitoje galvos pusėje. *CA* stebėsenos duomenims rinkti ir *VRx* apskaičiuoti realiuoju laiku naudota „*ICM+*“ programinė įranga (*Cambridge*, UK). *ABP* buvo matuojamas monitoriumi *Finapres Nova* (Enschede, Nyderlandai) (2.2.1 pav.). Statistinė duomenų analizė atlikta naudojant *IBM SPSS v23.0* programinį paketą. Visi kintamieji buvo apibrėžti ir apibendrinti naudojant aprašomąją statistiką, pateikti kaip vidutinės vertės ir standartiniai nuokrypiai (*SD*). Skirstinio normalumui įvertinti naudotas Shapiro–Wilk testas. Skirtumams tarp tęstinių kintamųjų ir dviejų nepriklausomų imčių skirtumams tarp grupių apskaičiuoti naudotas Manno ir Whitney U testas.

2.2.1 pav. *nCA* stebėsenos įranga. Neinvazinis ultragarsinis *TOF* stebėsenos prietaisas, susidedantis iš ant galvos montuojamo rėmo, kompiuterio su *ICM+* programine įranga *CA* indeksui (*VRx*) apskaičiuoti realiuoju laiku ir *nABP* stebėsenos prietaiso (adaptuota iš [10])

Lėtosios bangos, kurių periodas nuo 0,5 iki 2,0 min., atspindi smegenų kraujotakos autoreguliacijos aktyvumą. *TOF* duomenų rinkimo mėginių ėmimo dažnis buvo 50 Hz. Laikinam *VRx*(*t*) apskaičiuoti buvo naudojami dviejų minučių judantys lėtų *IBV*(*t*) ir *ABP*(*t*) lėtų bangų laiko langai [10]. *IBV* ir *ABP* duomenims išskirti buvo naudojamas juostinis filtras.

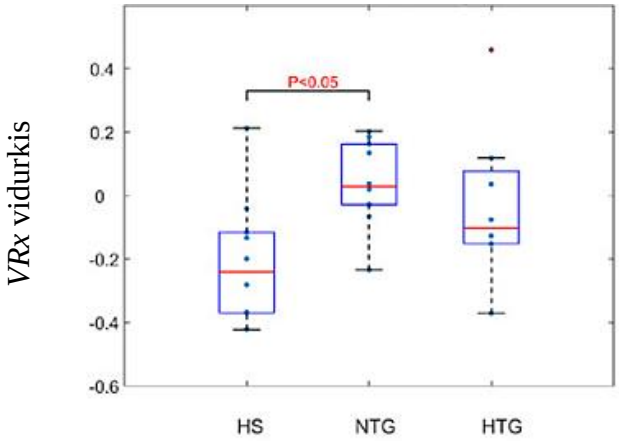
Kiekvieno paciento *CA* stebėjimo seansas truko iki 15 minučių. Pacientų buvo prašoma kartą per minutę Valsalvos manevrą, kad būtų išprovokuotos periodinės smegenų vazoreaktyvumo reakcijos ir susidarytų lėtos *ABP* bangos (1 min. trukmės), reikalingos *CA* vertinti. Iš kiekvieno tyrimo dalyvio matavimo seansų duomenų buvo nustatyti šie su *CA* susiję parametrai: vidutinė *VRx* reikšmė stebėjimo seanso metu, ilgiausio *CA* sutrikimo (angl. *Longest cerebral autoregulation impairment*, *LCAI*) trukmė ir *LCAI* dozė. *LCAI* trukmė buvo apskaičiuota pagal *VRx*(*t*) duomenis skirtingoms *VRx* ribinėms vertėms nuo *VRx* > 0 iki *VRx* > 0,9 su 0,1 žingsniu. Skiriamoji riba *VRx* = 0 yra teorinė matematinė riba, skirianti sutrikusią *CA* nuo nepažeistos *CA*. Teigiamo *VRx* vertės atspindi globalesnį sutrikusį smegenų kraujagyslių atsaką, kuris neužtikrina stabilios smegenų kraujotakos. *LCAI* dozė yra

parametras (plotas po *VRx*(*t*) kreive *LCAI* metu, kai *VRx* > 0), kuris išvedamas iš *LCAI* trukmės. Galiausiai visus 3 *CA* būklės parametrus palyginome tarp dalyvių grupių atlikdami Manno ir Whitney U testą, $p < 0,05$ reikšmės laikytos statistinio reikšmingumo įrodymu.

Rezultatai

28 tyrimo dalyviai sudarė 3 grupes: 10 NTG pacientų, 8 HTG ir 10 HS. Grupių *nCA* stebėsenos rezultatai – *VRx* ir jo išvestiniai parametrai bei statistinės analizės rezultatai pateikti 2.2.2–2.2.5 pav. ir 2.2.1–2.2.8 lentelėse. Pateikiama *LCAI* trukmė esant dviem *VRx* slenksčiams: *VRx* > 0 (matematinė riba, skirianti sutrikusią *CA* nuo nepažeistos *CA*) ir *VRx* > 0,4 (riba, kuriai esant gautas didžiausias statistinis reikšmingumas tarp atitinkamų dalyvių grupių).

Lyginant NTG ir HS grupių rezultatus nustatyti statistiškai reikšmingi skirtumai. Lyginant tarpusavyje bet kurias kitas grupes skirtumai nebuvo statistiškai reikšmingi.



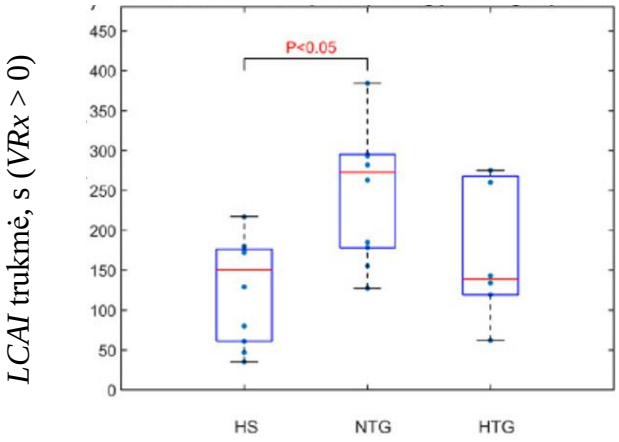
2.2.2 pav. Grupių *VRx* vidurkis (adaptuota iš [10])

2.2.1 lentelė. Grupių *VRx* vidurkis

Grupė	*VRx*	*SD*
HS	−0,179	0,220
NTG	**0,056**	**0,168**
HTG	−0,070	0,249

2.2.2 lentelė. *VRx* reikšmių palyginimas tarp grupių.
Manno ir Whitney U testo rezultatai, reikšmingumo slenkstis $p < 0,05$

Grupės	*p*
HS; NTG	**0,025**
HS; HTG	0,360
NTG; HTG	0,237



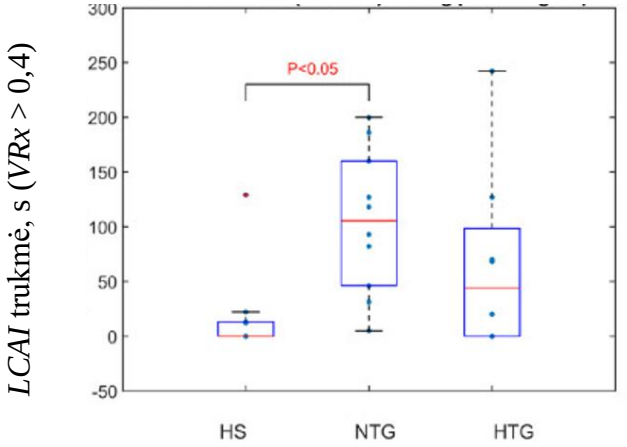
2.2.3 pav. *LCAI* trukmė, s (*VRx* > 0) (adaptuota iš [10])

2.2.3 lentelė. Grupių *LCAI* trukmė, s (*VRx* > 0)

Grupė	***LCAI***	***SD***
HS	127	66
NTG	**281**	**151**
HTG	231	218

2.2.4 lentelė. *LCAI* trukmės (*VRx* > 0) palyginimas tarp grupių. Manno ir Whitney U testo rezultatai; reikšmingumo slenkstis $p < 0,05$

Grupės	***p***
HS; NTG	**0,007**
HS; HTG	0,347
NTG; HTG	0,096



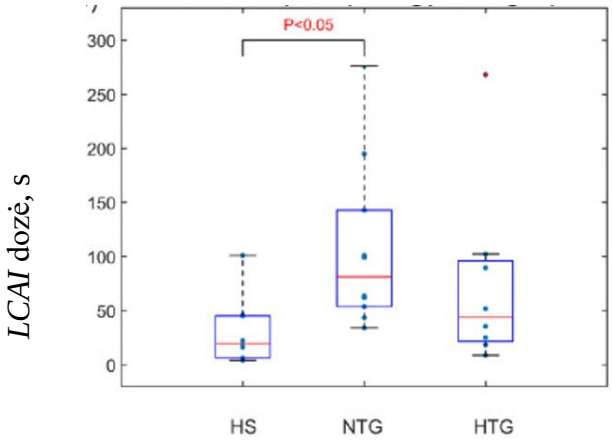
2.2.4 pav. *LCAI* trukmė, s (*VRx* > 0,4) (adaptuota iš [10])

2.2.5 lentelė. Grupių *LCAI* trukmė, s (*VRx* > 0,4)

Grupė	***LCAI***	**SD**
HS	18	40
NTG	**105**	**66**
HTG	65	84

2.2.6 lentelė. *LCAI* trukmės (*VRx* > 0,4) palyginimas tarp grupių. Manno ir Whitney U testo rezultatai; reikšmingumo slenkstis $p < 0,05$

Grupės	***p***
HS; NTG	**0,002**
HS; HTG	0,204
NTG; HTG	0,151



2.2.5 pav. *LCAI* dozė, s (*VRx* > 0) (adaptuota iš [10])

2.2.7 lentelė. Grupių *LCAI* dozė, s (*VRx* > 0)

Grupė	***LCAI* dozė**	***SD***
HS	31	29
NTG	**107**	**77**
HTG	75	85

2.2.8 lentelė. *LCAI* dozės (*VRx* > 0) palyginimas tarp grupių.
Manno ir Whitney U testo rezultatai; reikšmingumo slenkstis $p < 0,05$

Grupės	***p***
HS; NTG	**0,006**
HS; HTG	0,121
NTG; HTG	0,172

Rezultatų interpretacija

Tyrimo vaidmuo ir indėlis kitų tyrimų kontekste

Paprastai glaukoma laikoma akies nervo (ON) pažeidimo pasekme. ON skaidulos eina per sklerą iš *IOP* poveikio zonos į retrobulbarinę sritį, kuri yra *ICP* poveikio zona. Taigi akies nervo diską (OND) veikia du skirtingi slėgiai – santykinai didesnis *IOP* ir santykinai mažesnis *ICP*, kuriuos skiria LC [94]. Yra dvi pagrindinės glaukomą sukeliančių teorijų grupės [42]. Mechaninė teorija yra pagrįsta slėgiu ir teigia, kad padidėjęs *IOP* deformuoja LC ir sukelia akies nervo pažeidimą. Kraujagyslinė teorija teigia, kad sumažėjęs akių perfuzinis slėgis (*OPP*) ir akies vidaus kraujotaka RND srityje lemia tinklainės ganglinių ląstelių pažeidimą. Be to,

dėl kraujotakos sutrikimo LC pakinta ląstelės, todėl ji tampa jautresnė mechaniniam poveikiui. Tai rodo, kad šie du procesai yra neatsiejami vienas nuo kito [29, 95].

Padidėjęs *IOP* yra žinomas kaip pagrindinis kontroliuojamas glaukomos rizikos veiksnys ir BM [96], o *IOP* sumažinimas gali sulėtinti GL progresavimą. Tačiau *IOP* sumažinimas ne visada užkerta kelią ligos progresavimui. Nemažai tyrimų rodo, kad dalies POAG pacientų *IOP* yra normalus [97], ir tai yra tipiškas NTG požymis. Kita vertus, ilgalaikis *IOP* padidėjimas ne visada sukelia glaukomą [98, 99]. Tai suponuoja hipotezę apie daugiau veiksnių ir BM, prisidedančių prie glaukomos progresavimo. Darome prielaidą, kad vienas iš tokių veiksnių gali būti *CA*, kurią galima apibūdinti kaip smulkiųjų smegenų kraujagyslių (kapiliarų ir arteriolių) gebėjimą išsiplėsti arba susitraukti savo ribose, palaikant *CA*. Yra žinoma, kad kraujagyslių išsiplėtimą arba susitraukimą kontroliuoja kraujagyslę apgaubęs pericitų audinys. Pažeidus endotelio sluoksnį, ši funkcija sutrinka ir sukelia *CA* sutrikimą [100, 101]. Endotelio disfunkcija (ED) gali būti geras prognostinis veiksnys ir kelių ligų, įskaitant glaukomą, progresavimo biožymuo [102–104].

Hipotezė dėl *CA* vaidmens NTG figūruoja ir kituose tyrimuose [105–110]. Sutrikusi *CA* lemia tinklainės ganglinių ląstelių nykimą [111] ir regos lauko sutrikimus. Sisteminės kraujotakos didinimas gali pagerinti NTG pacientų regos lauką [112]. Endoteliui tenka svarbus vaidmuo kraujotakoje [112, 113]. Tyrimai parodė NTG pacientų ED, tačiau tiesioginių įrodymų nėra, todėl ryšys tarp ED ir NTG nėra iki galo aiškus.

Mūsų tyrimo rezultatai iškelia spragų užpildymo idėją ir logiškai įrodomo ryšio nustatymą sujungiant minėtus duomenis ir hipotezes. Atsižvelgiant į tai, kad ED gali sukelti *CA* sutrikimą ir kartu gali būti glaukomos biožymuo (tačiau trūksta įrodymų), galime daryti prielaidą, kad NTG sukelia ir *CA* sutrikimas, ir ED. Taigi mūsų rezultatai sustiprina ED ir GL priežastinio ryšio įrodymus. Šio tyrimo rezultatai taip pat galėtų pretenduoti į trūkstamos loginės sąsajos nustatymą, parodydami tiek NTG diagnozės faktų, tiek sutrikusios *CA* ryšį.

Pagrindinės įžvalgos ir tyrimo naujumas

Mūsų turimomis žiniomis, pirmą kartą pasaulinėje praktikoje glaukomos pacientų *CA* būklė buvo stebima ir lyginama su HS *CA* būkle naudojant *TOF* technologiją. *TOF* metodas leido patikrinti ir iš dalies įrodyti pirminę hipotezę apie glaukomos pacientų *CA* nestabilumą. Iš dalies dėl to, kad statistiškai reikšmingas skirtumas buvo nustatytas tik tarp NTG pacientų ir HS grupių rezultatų, ir dėl riboto pacientų, kurie buvo įtraukti į perspektyvinį bandomąjį tyrimą, skaičiaus. Mūsų tyrimas prisideda prie NTG (ir glaukomos apskritai) patogenezės ir ankstyvosios diagnostikos tyrimų, suteikia naujų žinių apie GL pacientų *CA*; pateikia idėjų tolesnėms *CA* sutrikimo GL atvejais studijoms. Tyrimas taip pat rodo, kad *VRx* ir kiti su *CA* susiję parametrai gali būti potencialūs NTG diagnostikos biožymenys.

Mūsų tyrime su *CA* susijusių parametrų (*VRx*, *LCAI* trukmė, *LCAI* dozė) matavimo rezultatų statistiškai reikšmingas skirtumas nustatytas Manno ir Whitney U testu tarp NTG ir HS grupių, o tarp kitų dviejų grupių derinių (HTG ir HS, NTG ir

HTG) reikšmingo skirtumo nenustatyta. Tai suponuoja mintį apie sutrikusią smegenų kraujotaką NTG atveju, keliant hipotezes apie NTG išsivystymo įtakos veiksnius, galimai susijusius labiau su *CA* sutrikimais negu su akių patologija.

Lygindami visus su *CA* susijusius parametrus nustatėme, kad *LCAI* trukmės skirtumas tarp NTG ir HS grupių (kai $VRx > 0,4$) yra statistiškai reikšmingiausias ($p = 0,002$). Tai taip pat kelia idėją, kad egzistuoja viena (ar kelios) optimalios pacientui būdingos *VRx* ribos, kurioms esant *LCAI* trukmės nustatymas turi didžiausią diagnostinį jautrumą ir specifiškumą. Tai siūlo galimos hipotezės kitiems tyrimams idėją: *LCAI* trukmės statistinio skirtumo reikšmingumo lygis skirtingoms *VRx* riboms gali būti susijęs su *CA* pablogėjimo lygiu ir prisidėti prie pagrindinės hipotezės (kad NTG yra susijęs su sutrikusia *CA*) įrodymo. *LCAI* dozės reikšmių palyginimas (tarp NTG ir HS grupių) demonstruoja $p = 0,006$ esant $VRx > 0$; o *LCAI* trukmės palyginimas (tarp NTG ir HS) demonstruoja $p = 0,007$ esant $VRx > 0$, tačiau $p = 0,002$ esant $VRx > 0,4$. Toks rezultatas kelia idėją, kad *LCAI* trukmė, išmatuota ties tam tikra riba, potencialiai gali būti informatyvesnis *CA* būklės parametras nei *LCAI* dozė.

Panašios slenkstinės ribos (0,4–0,5) buvo naudojamos ir kitiems neinvaziniams *CA* indeksams (slėgio reaktyvumo, vidutinio srauto, smegenų oksimetrijos), siekiant nustatyti *CA* sutrikimą [10].

Tyrimo apribojimai

Apribojimai: palyginti nedidelis įtrauktų dalyvių skaičius. Kitas apribojimas susijęs su tuo, kad nėra *CA* stebėsenos „auksinio standarto“ etalono, su kuriuo būtų galima palyginti *VRx* (kaip ir slėgio reaktyvumo indeksą (*PRx*), vidutinį smegenų srauto indeksą (*Mx*) ir kitus *CA* indeksus, naudojamus klinikiniuose tyrimuose su pacientais, patyrusiais TBI). *VRx* yra išvestinis parametras, suteikiantis informacijos apie tiriamojo objekto – paciento ir (arba) sveikos kontrolinės grupės *CA* būklę. *VRx* jautrumas ir metrologinės charakteristikos vis dar nepatvirtintos perspektyviniu daugiacentriu III fazės tyrimu. Tačiau jis suteikia diagnostinės informacijos, kurią galima nustatyti atlikus statistinę analizę. Perspektyvus intensyviosios terapijos skyrių pacientų *CA* įvertinimo tyrimas naudojant *VRx* parodė, kad *VRx* gali būti naudojamas kaip neinvazinis *CA* indeksas, lygiai taip pat kaip *PRx*, atspindintis integralią informaciją apie *CA* būklę visoje kaukolėje. Kita vertus, kadangi *TOF* pagrįstas metodas yra neinvazinis, jis taikytinas fiziologiškai sąmoningiems pacientams (tarp jų ir sergantiems glaukoma), kai invaziniai metodai yra sudėtingi arba neįmanomi. Reikalingi tolesni tyrimai su didesniu pacientų skaičiumi ir pakartotiniais matavimais stebėjimo metu.

NTG gydymo idėjos ir perspektyvos. Holistinis požiūris į smegenų sveikatą

Tyrimai rodo, kad fizinis aktyvumas yra palyginti paprasta, įgyvendinama, efektyvi ir perspektyvi gyvensenos dalis, siekiant užtikrinti kognityvinių funkcijų silpnėjimo pristabdymą [114].

Tyrime, paremtame Amerikos pensininkų asociacijos (angl. *American Association of Retired Persons*, AARP) ir Pasaulinės smegenų sveikatos tarybos (angl. *Global Council on Brain Health*, GCBH) rekomendacijomis dėl smegenų sveikatos išsaugojimo senstant, aptariami veiksniai, suteikiantys galimybių pagerinti smegenų sveikatą: psichinė gerovė, fiziniai pratimai, pažinimo veiklą skatinanti veikla, miegas, mityba, socialiniai ryšiai [115]. Pasaulinės sveikatos organizacijos Kognityvinių funkcijų silpnėjimo ir demencijos rizikos mažinimo rekomendacijose [116] išskiriamos kelios svarbios gyvensenos intervencijos, tokios kaip: fizinis aktyvumas, tabako vartojimo nutraukimas, mityba, priemonės dėl alkoholio vartojimo sutrikimų, kognityvinės, socialinės veiklos, svorio valdymas, hipertenzijos valdymas, diabeto valdymas. Aukščiausiu griežtumo lygiu išskiriamos šių sričių rekomendacijos: fizinio aktyvumo, tabako vartojimo nutraukimo, mitybos, hipertenzijos valdymo, diabeto valdymo.

Kaip ir *nICP* matavimo glaukomos pacientams studijos [9] apžvalgoje, vertinant NTG gydymo perspektyvas per *CA* ir smegenų sveikatos prizmę, būtina atsižvelgti ir į jogos pratimų potencialą. Nors randamų straipsnių antraščių, siejančių jogą ir smegenų sveikatą, yra palyginti nedaug, sprendžiant iš jų rezultatų, galima daryti išvadą, kad joga daro teigiamą įtaką ir smegenų sveikatai. 2015 m. publikuota literatūros apžvalga rodo, kad joga skatina smegenų alfa, beta ir teta bangų aktyvavimą, susijusį su pažinimo, atminties, nuotaikos ir nerimo pagerėjimu; nustatyta, kad pakaitinis kvėpavimas šnervėmis (pranajama) suaktyvina kontralateralinį smegenų pusrutulį ir taip suteikia neurokognityvinės naudos, padidėja tarphemisferinė darna ir simetrija [122]. Kitas tyrimas demonstruoja, kad jogos ir aerobikos pratimai gali sumažinti kai kuriuos išsėtinės sklerozės simptomus ir su tuo susijusius faktorius, tokius kaip gydymo išlaidos ir trukmė [123]. Gothe et al. savo tyrime daro išvadą, kad jogos elgesio intervencija gali būti perspektyvi siekiant sušvelninti su amžiumi susijusį ir neurodegeneracinį nuosmukį [124]. Joga, kaip kūrybinė gyvensenos intervencija, yra perspektyvi priemonė, gerinanti autizmo spektro sutrikimu (angl. *Autism spectrum disorder*, ASD) sergančių vaikų motorikos ir imitavimo įgūdžius [125]. 2019 m. paskelbtos tyrimų metaanalizės išvados rodo, kad jogos praktika gali turėti poveikį funkciniam DMN ryšiui, dorsolateralinės prefrontalinės žievės aktyvumui atliekant pažintines užduotis, hipokampo ir prefrontalinės žievės struktūrai, t. y. smegenų sritims, kuriose pastebimi reikšmingi su amžiumi susiję pokyčiai, todėl gali būti perspektyvi siekiant sušvelninti su amžiumi susijusį ir neurodegeneracinį nuosmukį [126]. Acabchuk et al. 2021 m. publikuotoje metaanalizėje apžvelgia jogos ir sąmoningumu pagrįstų elgesio intervencijų įtaką lengvo pobūdžio galvos traumų (angl. *Mild Traumatic Brain Injury*, mTBI) lėtiniams simptomams. Autoriai priėjo prie išvados, kad rezultatai pateikė daug žadančių įrodymų, jog meditacija, joga ir sąmoningumu pagrįstos intervencijos buvo susijusios su statistiškai reikšmingu, bet nedideliu simptomų, ypač nuovargio, depresijos ir gyvenimo kokybės, pagerėjimu, palyginti su kontrolinėmis grupėmis [127]. Kitos metaanalizės autoriai priėjo prie išvados, kad joga gali būti susijusi su mažesniu migdolinės smegenų skilties aktyvavimu ir mažesniu neigiamų jausmų, kylančių reaguojant į emociškai nerimą keliančius paveikslėlius, skaičiumi; jogos taikymas

gydant tam tikras neurologines ir psichosocialines būkles gali būti naudingas pacientams dėl galimo neuroplastinio poveikio [128].

Taigi, siekiant įvertinti jogos vaidmenį gydant glaukomą (ir ypač NTG), reikalingi papildomi jogos pratimų įtakos tyrimai, juos parenkant priklausomai nuo tiriamųjų grupės. Viena vertus, atsižvelgiant į tam tikrų pratimų (pvz., galva žemyn) keliamas rizikas GL (ypač HTG, dėl galimo *IOP* padidėjimo) pacientams, kita vertus, įvertinant pratimų įtaką smegenų sveikatai.

Poskyrio išvados

1. Glaukomos pacientų *CA* gali būti įvertinama vykdant *nCA* stebėseną bei apskaičiuojant *CA* parametrus: *VRx* indeksą bei jo išvestinius parametrus – *LCAI* trukmę ir *LCAI* dozę.

2. *CA* parametrų statistinių testų rezultatai rodo, kad CA_{NTG} ir CA_{HS} skiriasi statistiškai reikšmingai, t. y. CA_{NTG} yra sutrikusi ($detCA_{NTG}$), palyginti su CA_{HS}; skirtumai tarp CA_{HTG} ir CA_{HS} bei tarp CA_{HTG} ir CA_{NTG} atitinkamų parametrų verčių statistiškai nereikšmingi. Rezultatai suponuoja idėjas:

2.1. HTG atveju *CA* statusas artimas HS, t. y. *CA* nėra sutrikusi, todėl $detCA_{HTG}$ nepatenka į papildomų HTG biožymenų kandidatų gretas;

2.2. NTG priežastys gali būti susijusios labiau su sutrikusios *CA* negu su akies patologijos veiksniais; todėl *detCA* gali būti naudojamas kaip NTG biožymuo, suteikiant pridėtinę vertę NTG (ir apskritai glaukomos) diagnostikai.

3. Reikalingi didesnės apimties GL (ypač NTG) pacientų *nCA* matavimo tyrimai, siekiant įvertinti PSO rekomenduojamų gyvensenos intervencijų ir jogos pratimų įtaką smegenų sveikatai, sutrikusios *CA* normalizavimui ir NTG gydymui.

2.3. Žmogaus akies arterija kaip neinvazinio intrakranijinio slėgio stebėjimo jutiklis: skaitmeninis modeliavimas ir bandomasis *in vivo* tyrimas

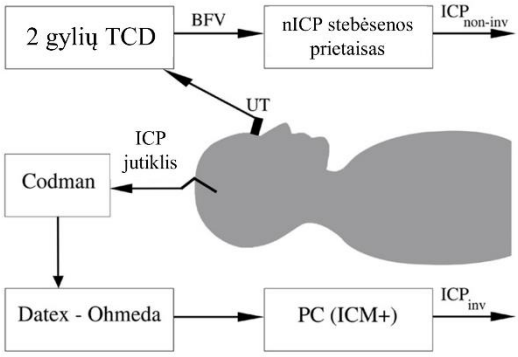
Originalus straipsnio pavadinimas: „Human ophthalmic artery as a sensor for non-invasive intracranial pressure monitoring: numerical modeling and *in vivo* pilot study“ [11].

Šios studijos tikslas – nedideliam dalyvių skaičiui ištirti *nICP* (*ICPnon–inv*) nuolatinės stebėsenos (iki 1 val. trukmės) galimybę su fiziologiškai sąmoningų pacientų (tarp jų ir sergančių glaukoma) stebėjimo perspektyva; papildomai naudojant OA kaip slėgio jutiklio koncepciją. *ICP* ir *IOP* vertės keičiasi paros laikotarpiu, veikiamos cirkadinių svyravimų, todėl trumpalaikiai šių slėgių matavimai tik tam tikru metu gali suteikti nepakankamai informacijos. Apžvalgoje aptariami tik esminiai momentai, nusakantys šį aspektą. Autoriaus indėlis: formalioji analizė ir pirminio teksto rašymas, diskutuojant su kitais bendraautoriais; papildomos išvados ir naujų biožymenų rekomendacijos, žvelgiant iš holistinio atskaitos taško.

Metodai

OA kaip slėgio jutiklio skaitmeninio modeliavimo metu siekta įvertinti, kokią įtaką OA kraujo tėkmės dinamikai daro stebėsenos procedūra. *COMSOL Multiphysics v 5.1.* programine įranga buvo sumodeliuota tiesi idealizuota OA, sprendžiant skysčio ir struktūros sąveikos (FSI) modelį.

Atlikus modeliavimą, Respublikinės Vilniaus universitetinės ligoninės Neurochirurgijos skyriuje metodas buvo kliniškai išbandytas *in–vivo*. Tyrime dalyvavo 6 TBI pacientai su implantuotais *ICP* stebėsenos jutikliais. Stebėsena buvo vykdoma invaziškai (*ICPinv*) ir neinvaziškai (*ICPnon–inv*) vienu metu, stebėjimo schema pavaizduota 2.3.1 pav. *ICPinv* buvo stebimas *Codman ICP* monitoriumi su kateterio antgalio jutikliu (*Johnson & Johnson Professional, Inc.*). Signalas buvo skenuojamas 300 Hz dažniu ir apdorojamas ICM+ v8.2 (Cambridge, UK) programine įranga, kartu su gyvybinių požymių monitoriumi (*Datex–Ohmeda, Inc.*, USA). *ICPnon–inv* stebėsenai skirtas 2 MHz ultragarsinis keitiklis buvo pritvirtintas prie individualiai pritaikyto galvos rėmo. Kraujo greitis IOA ir EOA segmentuose buvo registruojamas naudojant dviejų gylių TCD.



2.3.1 pav. Vienalaikio *ICPinv* ir *ICPnon–inv* stebėjimo sąranka. UT ultragarsinis keitiklis, BFV kraujo tėkmės greitis, TCD transkranijinis dopleris (adaptuota iš [11])

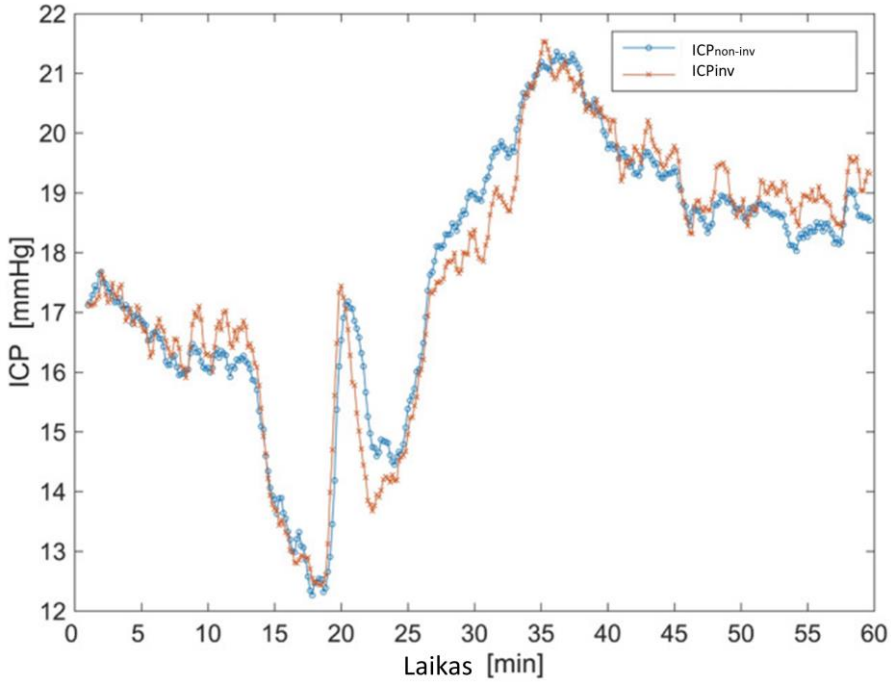
Atskiri *ICPinv* rodmenys buvo naudojami atliekant pradinį kiekvieno paciento matuojamo parametro kalibravimą, siekiant gauti *ICPnon–inv* vertes slėgio vienetais. Toliau vyko 1 val. nepertraukiama *ICPinv* ir *ICPnon–inv* stebėsena be pakartotinio kalibravimo. *ICPinv* ir *ICPnon–inv* duomenų pora buvo gaunama kas 10 s, ir per 1 val. susikaupė 360 duomenų taškų, kurie buvo apdorojami ir analizuojami. Blando ir Altmano bei tiesinei regresinei analizei atlikti naudota *MATLAB v.R2015b* programinė įranga.

Rezultatai

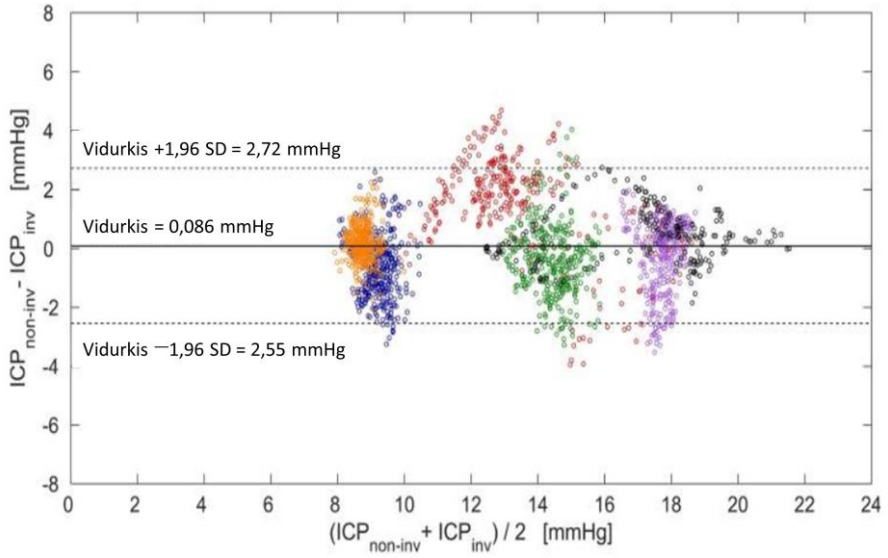
Kiekvienam pacientui buvo naudojama individuali tiesinė kalibravimo lygtis, siekiant gauti *ICP* vertes slėgio vienetais, po to jos lyginamos su *ICP* vertėmis.

Pašalinus TCD signalo artefaktus, buvo gautos 1928 poros duomenų galutiniam palyginimui. Bendras išmatuotų skirtumų tarp duomenų porų vidurkis ir *SD* yra 0,086 ± 1,34 mmHg. 2.3.2 pav. pateiktas pirmojo paciento (Nr. 1) 223 duomenų porų verčių grafikas. Abiem rodmenims išlyginti naudotas 60 s slenkančio vidurkio filtras. Didžiausias porinių duomenų taškų skirtumas buvo 1,61 mmHg. Visų 6 pacientų išmatuoti skirtumai tarp duomenų porų pateikti Blando ir Altmano diagramoje 2.3.3 pav. 6 pacientų duomenys atskirti 6 spalvomis: juoda Nr. 1, violetinė Nr. 2, mėlyna Nr. 3, raudona Nr. 4, oranžinė Nr. 5 žalia Nr. 6. Vientisa horizontali linija rodo bendrą skirtumų vidurkį, o dvi brūkšninės linijos – standartinį nuokrypį (SD) ± 1,96. Skirtumų kraštutinės reikšmės yra –3,94 ir 4,68 mmHg, o 95 % stebėjimų patenka į intervalą nuo –2,55 iki 2,72 mmHg.

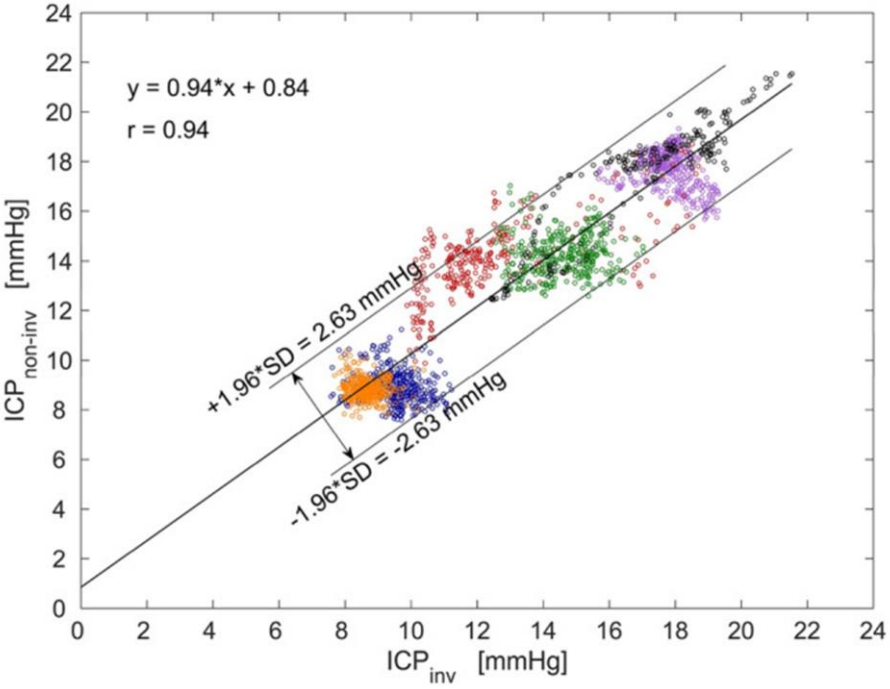
Regresinė analizė parodė, kad tarp duomenų, gautų naudojant dviejų gylių TCD ir Codman *ICP* monitorių, yra stiprus teigiamas ryšys (r = 0,94). Pacientų duomenys atskirti 6 spalvomis: juoda Nr. 1, violetinė Nr. 2, mėlyna Nr. 3, raudona Nr. 4, oranžinė Nr. 5 žalia Nr. 6 (2.3.4 pav.). Tiesinė lygtis $y = 0{,}94x + 0{,}84$ rodo, kad OA galima naudoti kaip tiesinį slėgio jutiklį, kurio nuokrypis (sisteminė paklaida) tiriamame *ICP* diapazone yra 0,84 mmHg.



2.3.2 pav. Paciento Nr.1 suporuotų *ICPinv* ir *ICPnon–inv* duomenų pavyzdys (adapt. iš [11])



2.3.3 pav. Skirtumo tarp duomenų porų pasiskirstymo (slėgio diapazone) diagrama (adaptuota iš [11])



2.3.4 pav. Visų duomenų taškų tiesinės regresijos grafikas (adaptuota iš [11])

Rezultatų interpretavimas

Invazinė *ICP* stebėsena jau kurį laiką taikoma TBI pacientams, tačiau *ICP* stebėsenos poreikis didėja ir oftalmologijos bei kosminės medicinos srityse [11]. Kadangi šių sričių pacientai fiziologiškai sąmoningi, stebėsenai tinka tik neinvazinės technologijos. Šiame tyrime ištyrėme galimybę naudoti OA kaip *ICP* slėgio jutiklį ilgalaikei trukmės *ICPnon–inv* stebėsenai, pagrįstai dviejų gylių TCD [11].

ICPnon–inv stebėsenos metodas parodė stiprią teigiamą koreliaciją (r = 0,94) su *ICPinv* duomenimis. Siekiant patikrinti hipotezę apie OA rezultatų tiesiškumą, pradiniam kalibravimui buvo naudojamos *ICPinv* vertės, t. y. neinvazinio dviejų gylių TCD duomenys konvertuojami į *ICPnon–inv* vertes slėgio vienetais. Regresinė analizė parodė, kad OA gali veikti kaip tiesinis *ICP* jutiklis tiriamame *ICP* diapazone.

Siūlomu metodu be pakartotinio kalibravimo galima stebėti *ICPnon–inv* iki vienos valandos. Pradiniam kalibravimui ir periodiniam perkalibravimui galėtų būti naudojamas *ICPnon–inv* momentinio matavimo metodas, pasižymintis kliniškai priimtinu tikslumu ir preciziškumu [11]. Šiuo atveju siūlomas metodas būtų visiškai neinvazinis ir būtų išvengta bet kokių invazinių procedūrų sukeliamų komplikacijų.

Poskyrio išvados

1. Rezultatai rodo, kad OA galima naudoti kaip linijinį natūralų *nICP* jutiklį ir kad *ICP* galima stebėti neinvaziškai iki 1 val. be pakartotinio kalibravimo.
2. Ši technologija galėtų padėti išspręsti fiziologiškai sąmoningų asmenų, įskaitant glaukomos pacientus, *nICP* stebėsenos ir diagnostikos problemas. Glaukomos pacientų ilgalaikė *nICP* stebėsena leistų tiksliau įvertinti *ICP*, palyginti su *nICP* trumpalaikiu matavimu, dėl cirkadinių *ICP* svyravimų, suteikiant pridėtinę vertę GL diagnostikoje. Naudojant *nICP* kaip biožyemenį, stebėsena įgalintų tiksliau jį įvertinti, palyginti su trumpalaikiu matavimu.
3. Reikalingi glaukomos pacientų neinvazinės ilgalaikės *nICP* stebėsenos tyrimai.

2.4. Ar gali normalaus slėgio smegenų vandenligės gydymas sukelti normalaus akispūdžio glaukomą? Šiuolaikinių žinių naratyvinė apžvalga

Originalus straipsnio pavadinimas: „Can the Treatment of Normal–Pressure Hydrocephalus Induce Normal–Tension Glaucoma? A Narrative Review of a Current Knowledge“ [12].

Šio straipsnio tikslas – naratyviai apžvelgti paskelbtą literatūrą apie NPH gydymo ir NTG galimą išsivystymo ryšį, pabrėžti neurooftalmologinio stebėjimo būtinybę pacientams, sergantiems šuntavimo būdu gydoma NPH. Autoriaus indėlis: dalies atrinktų straipsnių analizė, diskutuojant su kitais bendraautoriais; papildomos išvados ir naujų biožymenų rekomendacijos, žvelgiant iš holistinio atskaitos taško.

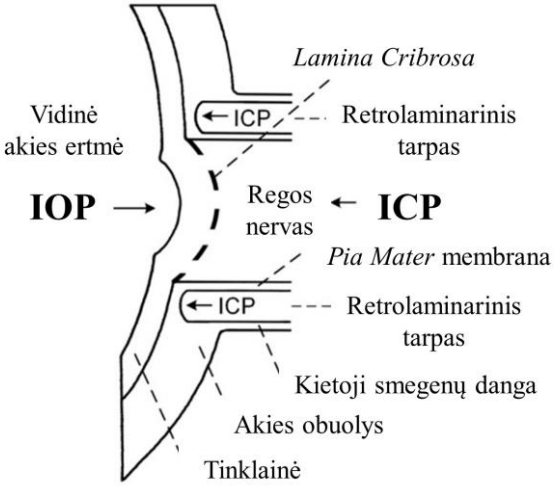
Straipsnyje apžvelgti šie aspektai ir šaltiniai:

1. patofiziologinis NTG ON pažeidimo mechanizmas;
2. NPH ir NTG ryšys;
3. perspektyviniai tyrimai;
4. retrospektyviniai tyrimai;
5. atvejų ataskaitos;
6. apžvalginiai dokumentai, kuriuose pateikiamos medicininės hipotezės;
7. paieška buvo vykdoma naudojantis Pubmed internetiniu resursu.

Rezultatai

Hipotezė apie ryšį tarp NPH gydymo naudojant šuntą *ICP* mažinti ir NTG išsivystymo patvirtinta apžvelgtuose retrospektyviuose tyrimuose, atvejų ataskaitose ir apžvalginiuose straipsniuose. Rezultatai sufleruoja idėją, kad neurologiniams pacientams (ypač šuntavimo būdu gydomiems NTG pacientams) reikėtų įvertinti ir pradėti naudoti apatinę saugios *ICP* vertės ribą. Jei taip, saugios viršutinės *ICP* ribos paradigma (kaip rekomenduojama neurochirurgijoje $ICP < 20$ mmHg arba $ICP < 22$ mmHg, o neurologijoje $ICP < 14{,}7$ mmHg [12]) turėtų būti modifikuota į saugaus *ICP* intervalo paradigmą, taikomą neurologijoje ir oftalmologijoje, siekiant išvengti NTG progresavimo.

IOP matavimas, nors ir netiesioginis, yra neinvazinis ir lengvai realizuojamas naudojant aplanacinį tonometrą. O *ICP* matavimas paprastai yra sudėtingas, nes, norint gauti patikimą *ICP* vertę, reikia atlikti invazines procedūras neurochirurginiu būdu. *nICP* matavimas leistų geriau valdyti pooperacinį šuntu gydomų pacientų gydymą ir paskatintų būsimus tyrimus, kuriais būtų ieškoma saugių apatinių *ICP* arba viršutinių $\Delta P \times t$ slenkstinių verčių. Siūlomi neinvazinių *ICP* vertinimo metodai. Buvo aptiktas tik vienas glaukomos pacientų tyrimas (aktualiai datai), kuriame buvo matuojamas *nICP* dviejų gylių TCD [56]. Šios neinvazinės *ICP* technologijos tikslumas, preciziškumas, diagnostinis jautrumas ir specifiškumas buvo išbandytas nepriklausomai tiriant įvairių grupių neurologinius pacientus; ateityje dviejų gylių TCD *nICP* matavimo technologijos turėtų leisti ieškoti saugių žemesnių *ICP* verčių slenksčių, kurie leistų gydyti NPH be NTG išsivystymo rizikos arba su minimalia rizika ir į klinikinę praktiką įdiegtų saugaus *ICP* intervalo paradigmą [12]. 2.4.1 pav. pavaizduota šuntavimu gydomos NPH LC veikiančių slėgių schema.



2.4.1 pav. LC veikiantys slėgiai NPH gydymo metu (adaptuota iš [12])

Nors per žemas *ICP* daro įtaką glaukomos vystymuisi, atsiranda publikacijų, rodančių, kad dar vienas papildomas fiziologinis mechanizmas pradėjo aiškėti kaip veiksnys, galintis turėti įtakos GL vystymuisi – būtent *CA*; ši tendencija palaiko mūsų tyrime [12] tikrintą hipotezę.

Poskyrio išvados

1. Egzistuoja ryšys tarp NPH gydymo šuntavimu ir NTG išsivystymo.
2. Saugaus viršutinio *ICP* slenksčio paradigma (pvz., rekomenduojama neurochirurgijoje *ICP* < 20 mmHg arba *ICP* < 22 mmHg, o neurologijoje *ICP* < 14,7 mmHg) turėtų būti pakeista į saugaus *ICP* intervalo paradigmą, taikomą neurologijoje ir oftalmologijoje, ypač šuntavimu gydomiems NPH pacientams ir NPH pacientams, sergantiems ir NTG, siekiant išvengti NTG progresavimo rizikos.
3. Nėra duomenų apie saugias mažesnes (konkrečiam NPH pacientui pritaikytas) *ICP* slenkstines vertes su minimalia NTG rizika. *nICP* matavimas ir reguliari oftalmologinė apžiūra gali padėti ieškoti tokių verčių.
4. Kai kurie duomenys rodo, kad *CA* gali turėti įtakos glaukomos patogenezei. Reikia NPH pacientų, kuriems yra NTG išsivystymo rizika, *nCA* stebėsenos perspektyvių tyrimų.

3. IŠVADOS

1. Tiek aukšto akispūdžio glaukoma (HTG), tiek normalaus akispūdžio glaukoma (NTG) sergančių pacientų statistiškai reikšmingai ($p < 0{,}05$) žemesnis už normalų (sveikų asmenų, HS) vidutinis intrakranijis slėgis *lowICP* ($nICP_{HTG}$ = 8,11 mmHg < $nICP_{NTG}$ = 9,42 mmHg < $nICP_{HS}$ = 10,73 mmHg), ypač kartu su aukštesniu už normalų vidutiniu akispūdžiu *highIOP* (IOP_{HTG} = 25,68 mmHg > IOP_{NTG} = 14,77 mmHg > IOP_{HS} = 13,77 mmHg), signalizuoja apie anormalų slėgių skirtumą *IOP*−*ICP*, galintį sukelti akytosios plokštelės (lot. *Lamina Cribrosa*, LC) deformaciją, kuri yra viena iš pagrindinių mechaninių priežasčių, sukeliančių pirminę atviro kampo glaukomą (ypač HTG). Todėl *lowICP* galėtų būti vertinamas kaip papildomas glaukomos biofizinis biožymuo (Nr. 1), signalizuojantis apie glaukomą (ypač HTG) arba jos vystymosi riziką. Toks netiesioginis neinvazinis LC deformacijos (arba jos rizikos) identifikavimas leistų įvertinti fizioterapinių akių procedūrų bei tikslingai parinktų jogos pratimų poreikį bei jų taikymo galimybes, normalizuojant LC formą po deformacijos ar net gydant glaukomą. Todėl tikslinga įtraukti *nICP* matavimą į glaukomos diagnostikos (ypač profilaktinės) protokolą, tuo suteikiant jai (ypač ankstyvajai) papildomą vertę.

2. HTG sergančių pacientų smegenų kraujotakos autoreguliacija (*CA*) nesiskiria nuo sveikų tiriamųjų (HS), o NTG pacientų *CA* yra sutrikusi; tą rodo:

2.1. NTG tūrinio reaktyvumo indekso vidurkio teigiama reikšmė (VRx_{NTG} = 0,056 > 0), kuri skiriasi nuo sveikų asmenų VRx_{HS} reikšmės (VRx_{HS} = −0,179) statistiškai reikšmingai (p = 0,025 < 0,05). O HTG sergančių pacientų (VRx_{HTG} = −0,070 < 0) skyrėsi nuo sveikų asmenų VRx_{HS} statistiškai nereikšmingai (p = 0,360 > 0,05);

2.2. NTG ilgiausio *CA* sutrikimo įvykio (*LCAI*) trukmė (esant VRx > 0: $LCAI_{NTG}$ = 281 s > $LCAI_{HTG}$ = 231 s > $LCAI_{HS}$ = 127 s) ir statistiškai reikšmingas jos skirtumas, palyginti su HS verte (p = 0,007 < 0,05); $LCAI_{HTG}$ skirtumas nuo $LCAI_{HS}$ statistiškai nereikšmingas (p = 0,347 > 0,05);

2.3. NTG ilgiausio *CA* sutrikimo įvykio dozės (*LCAId*) vertė (esant VRx > 0: $LCAId_{NTG}$ = 107 s > $LCAId_{HTG}$ = 75 s > $LCAId_{HS}$ = 31 s); ir statistiškai reikšmingas jos skirtumas, lyginant su HS verte (p = 0,006 < 0,05); $LCAId_{HTG}$ skirtumas nuo $LCAId_{HS}$ statistiškai nereikšmingas (p = 0,121 > 0,05).

Todėl *detCA* gali būti vertinama kaip papildomas glaukomos biofizinis biožymuo (Nr. 2), signalizuojantis apie normalaus akispūdžio glaukomą arba jos vystymosi riziką. *detCA* identifikavimas leistų įvertinti *CA* normalizavimo poreikį, siekiant suvaldyti NTG vystymąsi, pasiūlant pacientams holistiniu požiūriu į smegenų sveikatą paremtus sprendimus, tokius kaip Pasaulinės sveikatos organizacijos rekomenduojamos gyvensenos intervencijos, skirtos smegenų sveikatai gerinti, ir tikslingai parinkti jogos metodai. Tokie sprendimai aktualūs ir *ICP* normalizavimui, kadangi ir NTG atvejais buvo nustatytas *lowICP*. Todėl *nCA* matavimą tikslinga įtraukti į glaukomos diagnostikos (ypač profilaktinės) protokolą, tuo suteikiant jai (ypač ankstyvajai) papildomą vertę.

3. Nustatytas normalaus intrakranijinio slėgio smegenų vandenligės (NPH) gydymo šuntavimu ir glaukomos rizikos ryšys kelia idėją, kad, minėto gydymo metu, vietoj *ICP* saugios viršutinės vertės (neurochirurgijoje *ICP* < 20 mmHg arba *ICP* < 22 mmHg, o neurologijoje *ICP* < 14,7 mmHg) būtina naudoti saugaus *ICP* intervalą, įvertinantį ir apatinę *ICP* saugios vertės ribą, ir rekomenduoti pacientams reguliarius neinvazinius *ICP* matavimus bei oftalmologinę apžiūrą, kad, esant *nICP* žemiau apatinės intervalo ribos, galima būtų suvaldyti glaukomos riziką reguliuojant šuntą. Taip pat į NPH gydymo protokolą siūloma įtraukti papildomus minėtus glaukomos biožymenis: *lowICP* ir *detCA*. Analogiškai kaip ir *lowICP* bei *detCA* atvejais, NPH pacientams galima siūlyti holistiniu požiūriu į smegenų sveikatą paremtus sprendimus.

4. Pavyko pademonstruoti ryšį tarp glaukomos diagnozės ir mechaninių veiksnių *lowICP* ir *detCA*, naudojant santykinai portatyvius, mobilius ir nebrangius, pakankamai tikslius (klaidos tikimybė $p < 5\%$) ir efektyvius neinvazinius metodus, suformuluojant paradigmų patikslinimą:

4.1.a. dabartinė glaukomos paradigma: *highIOP* yra aukšto akispūdžio glaukomos biofizinis biožymuo; HTG yra liga, įtakojama vieno slėgio (*IOP*); NTG priežastys yra neaiškios.

4.1.b. patikslinta glaukomos paradigma: *highIOP* yra aukšto akispūdžio glaukomos biofizinis biožymuo; *lowICP* yra aukšto akispūdžio glaukomos ir normalaus akispūdžio glaukomos biofizinis biožymuo; *detCA* yra normalaus akispūdžio glaukomos biofizinis biožymuo; HTG yra liga, įtakojama dviejų slėgių (*IOP*, *ICP*); NTG yra liga, įtakojama trijų slėgių (*IOP*, *ICP*, *CA*);

4.2.a. dabartinė normalaus slėgio smegenų vandenligės gydymo šuntu paradigma: žemesnė už aukščiausią ribinę vertę *ICP* vertė yra saugi;

4.2.b. patikslinta normalaus slėgio smegenų vandenligės gydymo šuntu paradigma: per žema *ICP* vertė nėra saugi, nes gali sukelti glaukomos riziką; egzistuoja saugaus *ICP* intervalas, kurio ribose būtina užtikrinti *ICP*, norint suvaldyti glaukomos riziką.

Siūlomos tolesnių tyrimų idėjos

1. Naujų siūlomų biožymenų *lowICP* ir *detCA* įtakos glaukomai studija, tikrinanti atvirkštinį priežasties ir pasekmės ryšį, t. y. besiskundžiantiems regos sutrikimais pacientams, kuriems dar netirti glaukomos požymiai (ar net tiriant profilaktiškai), reikėtų matuoti *nICP* ir *nCA*, siekiant patikrinti *lowICP* ir *detCA*, ir tik po to atlikti oftalmologinę apžiūrą. Taip siekiant ištirti *lowICP* bei *detCA* ir GL diagnozės bei stadijos ryšį, identifikuoti GL riziką ankstyvojoje stadijoje (taip pat ir profilaktinės diagnostikos metu), kai nėra akivaizdžių GL požymių, matuojamų įprastiniais būdais, įeinančiais į GL diagnostikos protokolus.

2. Glaukomos pacientų *nIOP*, *nICP* ir *nCA* matavimų ir (arba) stebėsenos tyrimai surenkant kuo daugiau papildomų konkretaus paciento duomenų ir parametrų, kad tolesniame etape, panaudojant dirbtinio intelekto įrankius, būtų galima vykdyti visų įmanomų priežasties ir pasekmės ryšių paiešką (kurių gali nepastebėti žmogus) ir jų įvertinimą.

3. Fizioterapijos poveikio, HTG gydant LC formos normalizavimo būdu, tyrimai; jogos pratimų poveikio, siekiant normalizuoti *IOP* ir *ICP*, tyrimai; siekiant įvertinti jų įtaką *nIOP* ir *nICP* ir jau besivystančios glaukomos eigai arba galimos GL rizikai.

4. PSO rekomenduojamo fizinio aktyvumo ir kitų gyvensenos intervencijų (gerinančių smegenų sveikatą ir, galimai, tuo pačiu, *CA*), jogos pratimų įtakos tyrimai, siekiant įvertinti jų įtaką *nCA* ir *nICP* bei jau besivystančios GL eigai arba galimos GL rizikai.

5. Šuntavimo būdu gydomų NPH sergančių pacientų, kurių regai kyla glaukomos rizika, *nICP* ir *nCA* matavimų tyrimai, siekiant įvertinti jų įtaką jau besivystančios GL eigai arba galimos GL rizikai.

SUMMARY

1. INTRODUCTION

Scope, type and structure of the dissertation

This dissertation belongs to the field of medical measurements. Its topics include investigation of the additional biomarkers:

1. lower than normal intracranial pressure (lowICP);
2. deteriorated cerebral blood flow autoregulation (detCA);

and exploration of the potential for their inclusion into the diagnosis of glaucoma.

The dissertation is a conceptual and holistic summarisation based on four published articles. The topic of additional biomarkers for glaucoma diagnosis is analysed within the framework of the published articles, from a holistic point of view, providing ideas and insights for a more precise diagnosis and (noninvasive) treatment of glaucoma and its risk management during Normal Pressure Hydrocephalus (NPH) treatment, in the conclusions.

The doctoral thesis consists of the following parts: introduction, literature review, review of 4 articles, general conclusions, ideas for further research development, references, copies of 4 publications:

1. Deimantavicius M, Hamarat Y, **Lucinskas P**, Zakelis R, Bartusis L, Siaudvytyte L, Janulevicienė I, Ragauskas A. **Prospective Clinical Study of Non–Invasive Intracranial Pressure Measurements in Open–Angle Glaucoma Patients and Healthy Subjects**. Medicina (Kaunas). 2020 Nov 30;56(12):664. doi: 10.3390/medicina56120664.

2. Hamarat Y, Deimantavicius M, Dambrauskas V, Labunskas V, Putnynaite V, **Lucinskas P**, Siaudvytyte L, Simiene E, Stoskuviene A, Januleviciene I, Petkus V, Ragauskas A. **Prospective Pilot Clinical Study of Noninvasive Cerebrovascular Autoregulation Monitoring in Open–Angle Glaucoma Patients and Healthy Subjects**. Transl Vis Sci Technol. 2022 Feb 1;11(2):17. doi: 10.1167/tvst.11.2.17.

3. **Lucinskas P**, Deimantavicius M, Bartusis L, Zakelis R, Misiulis E, Dziugys A, Hamarat Y. **Human ophthalmic artery as a sensor for non–invasive intracranial pressure monitoring: numerical modeling and *in vivo* pilot study**. Sci Rep. 2021 Feb 26;11(1):4736. doi: 10.1038/s41598–021–83777–x.

4. Hamarat Y, Bartusis L, Deimantavicius M, **Lucinskas P**, Siaudvytyte L, Zakelis R, Harris A, Mathew S, Siesky B, Janulevicienė I, Ragauskas A. **Can the Treatment of Normal–Pressure Hydrocephalus Induce Normal–Tension Glaucoma?** A Narrative Review of Current Knowledge. Medicina (Kaunas). 2021 Mar 3;57(3):234. doi: 10.3390/medicina57030234.

Relevance of the problem and importance of research

Vision is the dominant human sense that underpins society, playing a crucial role in every aspect of life, and its disorders have serious consequences. Eye diseases such as cataracts, glaucoma (GL), etc. can lead to visual impairment and blindness.

Glaucoma is a group of eye diseases that cause damage to the optic nerve, which leads to impairment and/or loss of vision; GL is the 2nd leading cause of blindness after cataract and the 1st leading cause of irreversible blindness in the world; the prevalence of blindness due to GL is about 12.3% [1], whereas the prevalence of GL in the world population aged 40 years and over is around 3–5% [2].

Worldwide, approximately 64 million people have glaucoma [3], of whom 6.9 million (10.9%) suffer from moderate to severe visual impairment [4]. The *World Health Organisation* (WHO) estimates that, in 2020, there were 76 million people aged 40–80 with glaucoma [5], and this number could increase to 112 million by 2040 [1]. Thus, the need for eye care worldwide will increase dramatically and will become a challenge for health systems [5].

According to the WHO, visual impairment caused by GL is incurable and cannot be corrected. However, there are effective treatments that can delay or prevent the progression of the disease if diagnosed early and in time [5].

There are many criteria for the classification of GL, the most important of which are that GL may be primary or secondary; open or closed angle; high intraocular pressure glaucoma (high tension glaucoma, HTG) or normal intraocular pressure glaucoma (normal tension glaucoma, NTG). Primary open–angle glaucoma (POAG) is the most common worldwide.

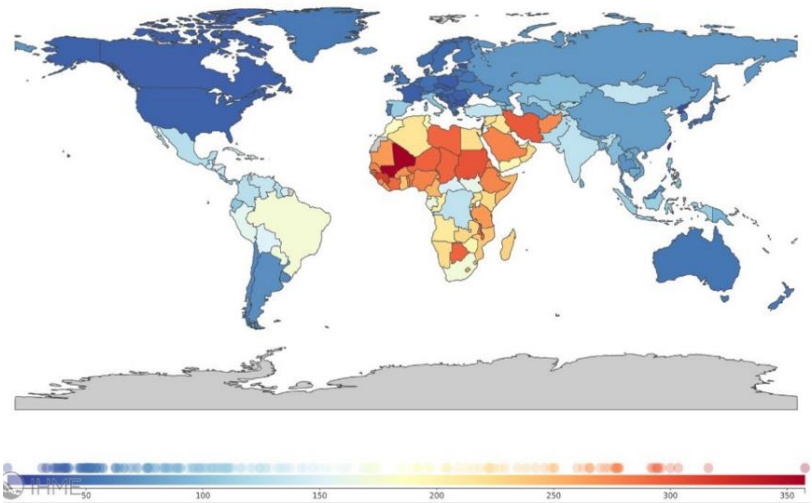


Figure 1. Geography of GL prevalence, cases per 100,000 population (adapted from [6])

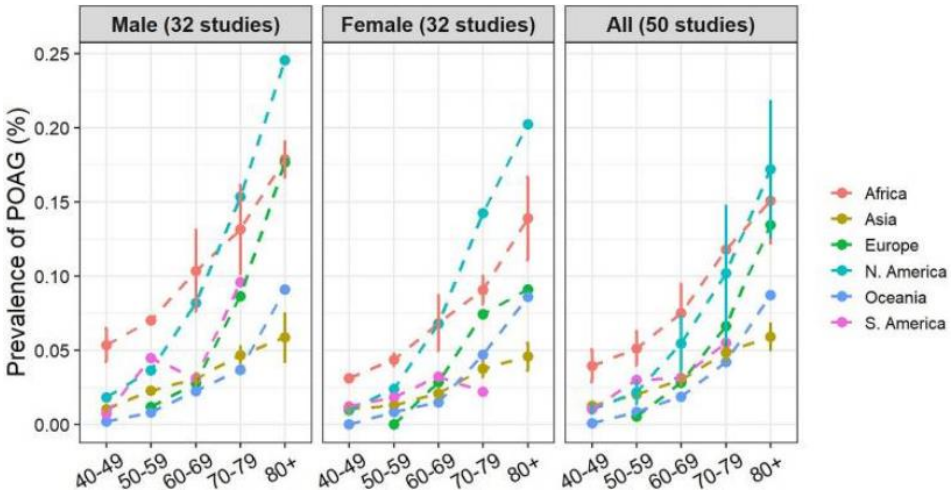


Figure 2. Global prevalence of POAG in different age groups, % (adapted from [7])

Recently, it has been hypothesised that GL may also develop as a consequence of treatment for hydrocephalus (CH) [12]. CH comprises a heterogeneous group of pathologies characterised by abnormal dilation of the cerebral ventricles. CH is most prevalent in Asia (Figure 3). Untreated CH can lead to progressive neurological injury and death, but early diagnosis and surgical intervention can lead to complete disappearance of the symptoms [8]. In the normal pressure CH (NPH), the ICP is within normal limits. This thesis involves only NPH type of CH.

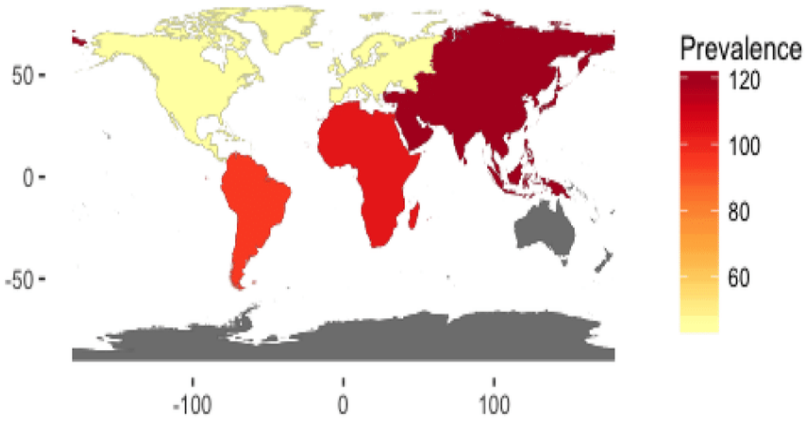


Figure 3. Prevalence of CH (per 100,000 population) in children and elderly populations (adapted from [8])

NPH is a neurological disorder common in adults and geriatric patients, with symptoms including enlarged cerebral ventricles, clinical gait disturbances, incontinence, and cognitive decline [12]. The most popular treatment for NPH is

ventriculoperitoneal shunt to drain excess cerebrospinal fluid (CSF). The procedure is performed in approximately 5.5 patients per 100,000 population each year. The problem is that draining CSF reduces ICP, which increases the risk of GL.

This thesis contributes to the global GL problem by addressing the topics of GL diagnosis, management, and improvement of the effectiveness of treatment by adding 2 additional biomarkers (BM) for HTG and NTG diagnosis and NPH treatment.

Scientific–technological problem

Can technological developments help improve the management (and even treatment) of glaucoma (and its risks) by improving its diagnosis by adding new biomarkers?

Working hypothesis

The management of glaucoma (and its risks): diagnosis, delay of its development and, prospectively, its treatment, can be improved by technological development, adding value to its diagnosis by adding two new biomarkers to the IOP measurement routine in ophthalmology:

a) by noninvasive measuring of ICP (nICP) to check whether it is lower than normal (lowICP, biomarker No. 1), indirectly assessing the deformation (or risk of it) of the Lamina cribrosa (LC) due to the abnormal IOP−ICP pressure difference;

b) by noninvasive monitoring of CA (nCA) to check whether it is deterioriated (detCA, biomarker No. 2);

c) in the case of NPH, refining the paradigm of safe low ICP by upgrading it to the paradigm of a safe ICP range.

Aim and objectives

Aim of the study: to test the working hypothesis that the treatment of GL can be improved by adding 2 biomarkers to GL diagnosis.

The following objectives were formulated to achieve the aim:

1. to interpret and summarise the data of measured nICP in HTG and NTG patients and healthy controls (HS) and to compare the results among all groups; to investigate the potential for long–term monitoring of nICP; to investigate the potential for incorporating nICP as a new BM No. 1 in the GL diagnostic process and to explore the potential for improving GL treatment;

2. to interpret and summarise nCA parameters measured in HTG patients, NTG patients and HS groups by using a non–invasive CA monitoring method based on ultrasound's time of flight (TOF) measurements (*Vittamed 505*) and the arterial blood pressure (*Finapres*) measurements for the calculation of CA parameters; to compare

the results among the 3 groups in terms of CA impairment; to investigate the feasibility of including an additional biomarker, detCA measurement, in the diagnosis of glaucoma, and to explore the possibility of improving the management of glaucoma (or its risk) by suggesting ideas for treatment;

3. to perform a narrative review of the literature regarding the potential for GL risk as a consequence of ICP reduction during NPH treatment by shunt; to investigate the feasibility of incorporating measurement of the additional biomarkers such as lowICP and detCA into the NPH treatment process to improve glaucoma risk management.

Logic of the research and articles

The research reviewed in this dissertation and the articles published on the basis of it are logically linked. Two main research studies and two complementary studies were carried out in order to meet the objectives of the thesis (Figure 4). The division of subjects into 3 groups (HTG patients, NTG patients and HS subjects) was known *a priori*.

1. A prospective study of nICP measurements in GL patients was designed to test part a) of the working hypothesis [9]. The results of the study showed that, although the difference in nICP between any 2 groups was statistically significant, the results of the comparison between the HTG and HS groups suggested that, whereas in HTG, lowICP may influence the development of HTG (due to LC damage), in NTG, other factors besides lowICP may be present, e.g. an impaired CA.

2. Therefore, to test part b) of the working hypothesis, a prospective follow–up study of nCA in GL patients was performed [10]. CA status was assessed by comparing the mean values of the volumetric reactivity index (VRx) and its derivative parameters among all 3 groups.

3. An additional study of the modelling and *in vivo* validation of nICP monitoring [11] was performed to assess the influence of circadian variations in ICP and the potential for long–term monitoring of nICP.

4. A narrative review of the literature [12] was performed to evaluate the idea of the risk of developing glaucoma (due to ICP lowering) during normal pressure hydrocephalus (NPH) treatment with bypass surgery; and the idea of measuring nICP and nCA in NPH patients.

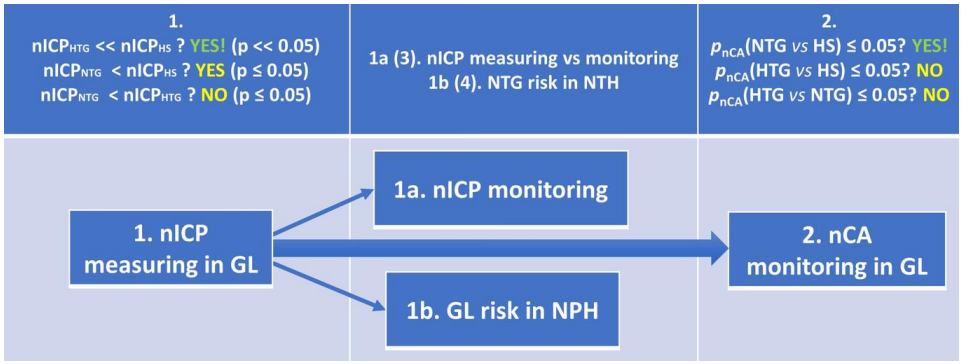


Figure 4. Logic of 2+2 studies and articles.
1. Measurement of nICP in GL patients (influence of GL on ICP); 2. Monitoring nCA in GL patients (influence of GL on CA); 1a (3). nICP long–term monitoring (influence of ICP circadian variations); 1b (4). GL risk in the treatment of NPH by bypass surgery

Scientific novelty

1. Two additional non–invasively measured biomarkers have been proposed with added value for ophthalmic and neurological diagnostics:

1.1. For HTG and NTG cases, in addition to the classical glaucoma biomarker – higher than normal intraocular pressure (highIOP) used in ophthalmology, the measurement of nICP, verifying the lowICP status (new BM No. 1), at the Lamina Cribrosa (LC) has been proposed to indirectly investigate the influence of abnormal difference IOP−ICP on the deformation of the LC; ideas for the noninvasive treatment of HTG (through the restoration of LC shape after deformation), based on physiotherapy procedures, selected Yoga methods and holistic approach to brain health have been proposed.

1.2 For NTG case, in addition to measuring IOP, monitoring the nCA to check the status of the detCA has been proposed (new BM No. 2); ideas for the treatment of NTG (through the normalization of CA) based on WHO recommendations and a holistic approach to brain health have been proposed.

1.3 For the treatment of NPH case, in addition to the use of a ventricular shunt, the measurement of nICP and monitoring of nCA (BM No. 1 and BM No. 2) have been proposed to assess the risk of glaucoma and to recommend ophthalmological examination of patients if necessary.

2. Proposed paradigm corrections.

2.1 Current paradigm for glaucoma: glaucoma is a ‘1–pressure disease’, highIOP is a biomarker for HTG, reasons of NTG are unclear; proposed paradigm:

glaucoma is a ‘2 or even 3–pressures disease’, highIOP is a biomarker for HTG; lowICP is a biomarker for both HTG and NTG; detCA is a biomarker for NTG;

2.2 The current paradigm for NPH treatment: low ICP is safe; the proposed paradigm: too low an ICP can lead to a risk of glaucoma; there is a range of safe ICP within which ICP must be maintained.

3. The feasibility of non–invasive monitoring of nICP and nCA in patients with sufficient accuracy for clinical practice has been confirmed.

Methods

1. Measurements of nICP in GL (HTG and NTG) patients and HS groups were performed with a 2–depth Doppler *Vittamed 205*, developed at KTU Health Telematics Science Institute (HTSI). Patients were divided into HTG and NTG groups by the specialists of the Eye Diseases Clinic (EDC) of LSMU Kaunas Clinics. nICP was measured in the EDC, together with HTSI specialists. The results were compared among the groups, *IBM SPSS Statistics* software *v23.0* package was used to process the results.

2. The nCA monitoring in GL (HTG and NTG) patients and HS groups was performed by using a *Vittamed 505* cerebrovascular autoregulation monitor in combination with the *Finapres* non–invasive arterial blood pressure (ABP) monitor. nCA was assessed by calculating the VRx as the correlation coefficient between intracranial bood volume (IBV) and ABP slow waves; and the derivative parameters of VRx, such as the longest CA impairment event (LCAI) duration and LCAI dose.

3. The modelling of the ophthalmic artery blood flow and nICP measurements was performed at the Lithuanian Energy Institute using *COMSOL Multiphysics software v5.1* software package. *In vivo* validation was performed at the neurosurgical department of Vilnius Clinical Hospital; invasive ICP was monitored by using a *Codman ICP* monitor with a catheter tip sensor and *ICM+ v8.2*; non–invasive ICP was monitored by using a 2–depth *Vittamed 205* transcranial doppler developed by STMI.

4. A narrative review of the literature on potential GL risk in shunted NPH patients was performed in the *Pubmed* online database.

Practical relevance of the results

The results of the 4 studies analysed in this thesis contribute to the refinement of the diagnosis of HTG and NTG; they add value by proposing 2 new biomarkers, lowICP and detCA, which can be measured non–invasively in a specific patient by using mobile and relatively inexpensive equipment. The introduction of additional

glaucoma biomarkers in GL diagnostics is in line with the trend towards precision medicine [14] and could contribute to slowing down or even curing the development of glaucoma, by implementing HTG and NTG treatment ideas based on the above BMs, respectively: restoration of LC normal shape by negative pressure, after deformation, tailored Yoga exercises (for HTG), and restoration of normal CA by lifestyle interventions, exercises (for NTG); and could also contribute to glaucoma risk management in NPH.

Claims to be defended

1. The results of the non–invasive measurements of intracranial pressure (nICP) study showed that the nICP is lower than normal (of HS) in patients with (especially) high–tension glaucoma (HTG) as well as normal–tension glaucoma (NTG); a lower than normal nICP value (lowICP) signals an abnormal IOP−ICP pressure difference, which may lead to LC deformation and glaucoma risk, and can therefore be seen as an additional biomarker for HTG and NTG, thus adding value to the diagnosis of glaucoma (especially HTG) and suggesting ideas for non–invasive treatment.

2. The results of the non–invasive cerebral blood flow autoregulation (nCA) monitoring study showed that NTG patients have impaired CA, whereas HTG patients do not have impaired CA; impaired CA (detCA) status may be seen as an additional biomarker for NTG, thus adding value to the diagnosis of glaucoma (especially NTG) and suggesting ideas for non–invasive treatment.

3. The results of the study on glaucoma risk in the treatment of normal pressure hydrocephalus (NPH) imply the need to use a safe ICP range instead of a safe ICP upper threshold; and to recommend that patients should have regular nICP and nCA measurements and regular ophthalmological examinations to assess and manage glaucoma risk.

Dissemination of results

The results of the study have been published in 4 articles [9–12] in WoS (IF, Q1–Q2) journals and presented at 4 international scientific conferences.

2. OVERVIEW OF THE ARTICLES

General Introduction

The summary of the 4 articles reflects the results of the 4 studies with the aim of interpreting them and analysing from a holistic perspective the possibilities of including additional biomarkers to add value to GL diagnosis and treatment. The main (2.1, 2.2) and the additional (2.3, 2.4) studies cover the following aspects:

1. Measurement of nICP in HTG and NTG patients and HS and comparison of the results among the groups to test part (a) of the working hypothesis;
2. Monitoring of nCA in HTG and NTG patients and HS and comparison of the results among the groups to test part (b) of the working hypothesis;
3. Study on the feasibility of long–term monitoring of nICP;
4. Study on the risk of NTG due to decreasing ICP during NPH treatment to test part (c) of the working hypothesis.

2.1 Prospective Clinical Study of Non–Invasive Intracranial Pressure Measurements in Open–Angle Glaucoma Patients and Healthy Subjects

The aim of this study was to evaluate the differences in nICP among GL patients (HTG and NTG) and healthy subjects (HS) groups. The overview discusses the main aspects related to the working hypothesis. Author contributions: drafting the original manuscript, including analysis of the results and the literature, in discussion with the co–authors; additional conclusions and recommendations for the new biomarkers and treatment ideas for HTG from the holistic point of view.

Results

Data from 217 subjects (95 NTG, 60 HTG, 62 HS) were included in the statistical analysis. NTG patients had a significantly ($p < 0.05$) lower IOP compared with HTG patients, whereas HS patients had a significantly ($p < 0.05$) lower IOP compared with HTG patients (Figure 5).

Tukey's test (0.05 level of significance) demonstrated the following results for the mean nICP between groups: $nICP_{NTG}$ (9.42 ± 2.83 mmHg) was significantly ($p = 0.007$) lower than $nICP_{HS}$ (10.73 ± 2.16 mmHg); $nICP_{HTG}$ (8.11 ± 2.68 mmHg) was significantly ($p = 0.008$) lower than $nICP_{NTG}$ (9.42 ± 2.83 mmHg) and significantly ($p < 0.001$) lower than $nICP_{HS}$ (10.73 ± 2.16 mmHg). The results are shown in Figure 6.

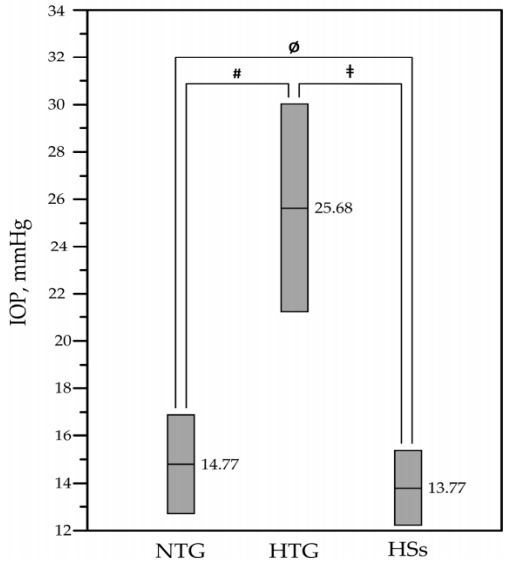


Figure 5. Mean IOP values with standard deviation for NTG, HTG and HS groups.
Ø – statistically significant difference ($p < 0.05$) of mean IOP between NTG and HS;
– statistically significant ($p < 0.05$) of mean IOP difference between NTG and HTG;
≠ – statistically significant difference ($p < 0.05$) of mean IOP between HTG and HS

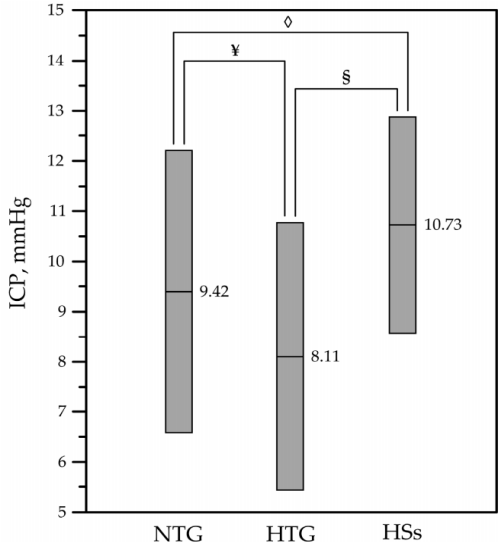


Figure 6. Mean nICP values with standard deviation for NTG, HTG and HS groups.
◊ – statistically significant difference ($p = 0.007$) of mean ICP between NTG and HS;
¥ – statistically significant difference ($p = 0.008$) of mean ICP between NTG and HTG;
§ – the difference is statistically significant ($p < 0.001$) of mean ICP between HTG and HS

Table 1. Comparison of mean nICP values between groups;
Tukey's test results at 0.05 significance level

Groups	P	nICP difference
NTG vs HS	0.007	significant
HTG vs NTG	0.008	significant
HTG vs HS	**0.001**	significant

Ideas and perspectives for the treatment of HTG

HTG is currently treated by lowering IOP by medical and surgical means, but medication only slows down the progression of the disease, and invasive procedures are still risky [81]. Against this background, the ideas and research of American ophthalmologist John Berdahl, MD & Colleagues stand out in particular, with publications from 2018 to 2021 demonstrating a new trend in the potential non–invasive treatment of HTG involving ocular physiotherapy procedures based on pressure exercise [80–87]. For the very first study in healthy subjects, a portable mobile multi–pressure dial (MPD) consisting of a pump connected via a hose to a negative pressure (vacuum) 'swimmer's' goggles that envelops the eyes was developed and used (Figure 7).

Figure 7. MPD pressure regulator (adapted from [80])

The air pump of the regulator causes a negative pressure in the eye area, resulting in a reduction of intraocular pressure. In a pilot study of 30 healthy subjects, the right eye was exposed and examined and the left eye used as a control. The results [80] show a decrease in IOP in both eyes already on the first ('zero') day. Measurements of all parameters, including IOP, were taken before MPD was applied and were repeated immediately after its removal. After the adjustment of MPD, the negative pressure in the subject's eye was gradually increased to –15 mmHg, a value that was maintained for 30 min and then slowly reduced to the baseline. After the

removal of the device (day 0), baseline measurements were immediately repeated. Subjects returned for a repeat test within a week (days 6–8). At the 1 week post–test, both subjects and controls showed a statistically significant decrease in ocular IOP, but its clinical significance has not yet been established. No adverse events were observed, and the participants tolerated MPD well. Key safety parameters remained stable after short–term exposure. The favourable safety results of this study confirm the safety profile of MPD and encourage further investigation of this device and method as a potential treatment for GL.

The further studies are devoted to development of the initial idea: safety, increase of statistical robustness, modelling [81–87].

Another potentially effective way to reduce IOP is through some yoga techniques. In the recent decades, there has been a growing body of research, evidence and articles on the impact of yoga on health. A search for the keyword 'yoga' in *Pubmed* e–resource shows that the earliest studies date back to 1948, but the number of publications has increased exponentially since the 2000s [117]. The results of studies measuring the effect of yoga on IOP in GL patients suggest that yoga can both increase and decrease IOP, depending on the type of exercises chosen. The results of a pilot study by Jasien et al. showed that head–down yoga exercises induced a statistically significant and rapid increase in IOP shortly after the start of the exercises; and a decrease shortly after the cessation of the exercises [118]. Another study demonstrated that yoga and meditation caused a persistent decrease in the IOP–related profile, but none of the associated changes were statistically significant [119]. The study by Dada et al. states that meditation has been shown in previous studies of GL patients to reduce IOP, stress biomarkers, improve cerebral oxygenation, along with the quality of life, and that this is the first study to show that mindfulness–based stress reduction (MBSR) is a useful tool for reducing IOP. MBSR can improve optic nerve perfusion measured by optical coherence tomography–angiography; MBSR can be recommended as an adjunct treatment to medical therapy to increase ON head perfusion and reduce IOP, which may reduce glaucoma progression [120]. Kulkarni et al. found that certain pranayama techniques (right and left nostril breathing, alternate nostril breathing) were safe and had no adverse effect on increasing IOP in healthy subjects; they may also have a beneficial effect on reducing IOP [121].

2.2 Prospective pilot clinical trial of non–invasive monitoring of cerebrovascular autoregulation in patients with open–angle glaucoma and healthy subjects

In this study, for the first time, non–invasive ultrasound techniques were applied to investigate the dynamics of CA in three groups: NTG, HTG and HS, and to compare the results of all groups against each other. Author contributions include data analysis, full writing of the first version of the manuscript in discussion with the

other co–authors; extended interpretation of the results, 2 attempts to submit to free WoS journals; additional conclusions and recommendations for new biomarkers and treatment ideas for NTG from a holistic perspective.

Results

The 28 study participants comprised 3 groups: 10 NTG patients, 8 HTG and 10 HS. The results of the nCA monitoring of the groups, i.e. the VRx and its derived parameters, and the results of the statistical analysis are shown in Figures 8–11 and Tables 2–5. The duration of LCAI at two VRx thresholds is presented: VRx > 0 (the mathematical threshold separating impaired CA from intact CA) and VRx > 0.4 (the threshold at which the highest statistical significance was obtained between the respective groups of the participants).

Statistically significant differences were found when comparing NTG and HS. The differences were not statistically significant when comparing any of the other groups.

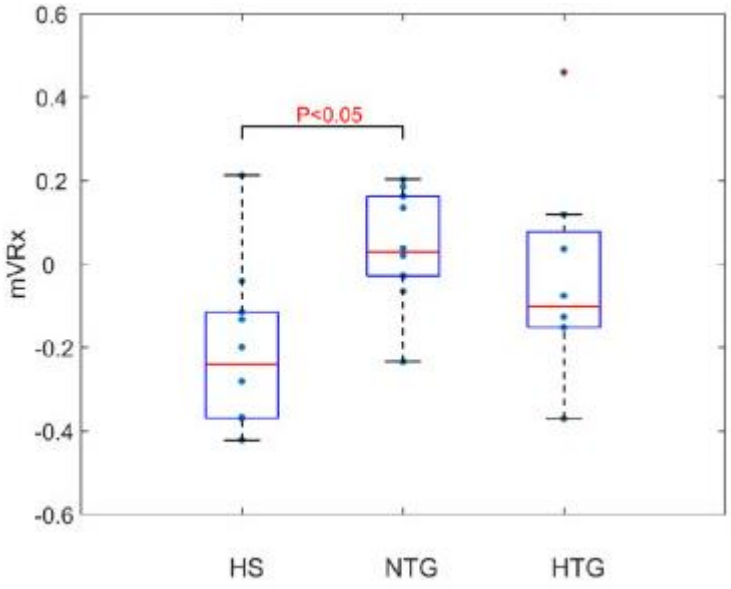


Figure 8. Mean VRx between groups (adapted from [10])

Table 2. Comparison of the results of the Mann–Whitney U test for VRx values between groups; significance threshold P < 0.05

Groups	P
HS; NTG	**0.025**
HS; HTG	0.360
NTG; HTG	0.237

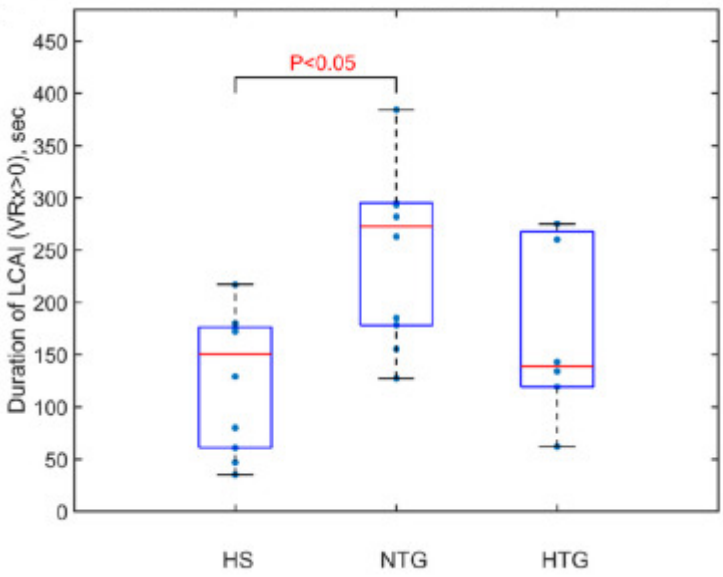


Figure 9. LCAI duration, s (VRx > 0) (adapted from [10])

Table 3. Comparison of Mann–Whitney U test results for LCAI duration (VRx > 0) between groups; significance threshold P < 0.05

Groups	**P**
HS; NTG	**0.007**
HS; HTG	0.347
NTG; HTG	0.096

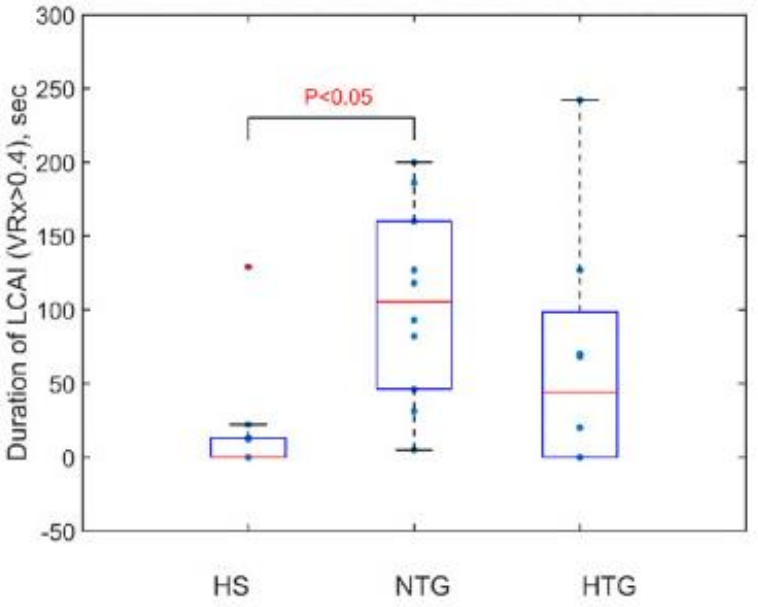


Figure 10. LCAI duration, s (VRx > 0.4) (adapted from [10])

Table 4. Comparison of Mann–Whitney U test results for LCAI duration (VRx > 0.4) between groups; significance threshold P < 0.05

Groups	**P**
HS; NTG	**0.002**
HS; HTG	0.204
NTG; HTG	0.151

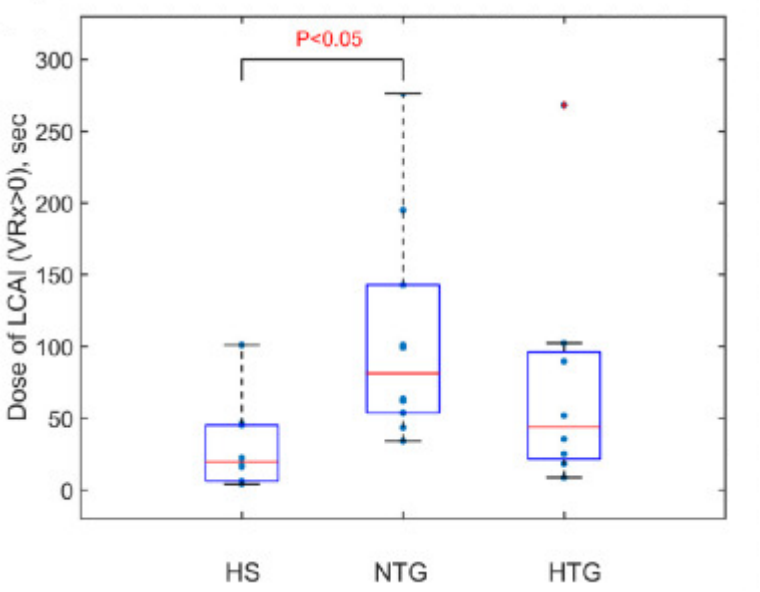


Figure 11. LCAI dose, s (VRx > 0) (adapted from [10])

Table 5. Comparison of Mann–Whitney U test results for LCAI dose (VRx > 0) between groups; significance threshold P < 0.05

Groups	P
HS; NTG	**0.006**
HS; HTG	0.121
NTG; HTG	0.172

Ideas and perspectives for the treatment of NTG. A holistic approach to brain health

Research shows that physical activity is a relatively simple, feasible, effective and viable part of a lifestyle to ensure that cognitive decline is slowed [114].

A study based on the *American Association of Retired Persons* (AARP) *Global Council on Brain Health* (GCBH) recommendations on maintaining brain health as we age discusses factors that offer opportunities to improve brain health: mental well–being, exercise, cognitive–enhancing activities, sleep, nutrition, and social relationships [115]. The *World Health Organisation*'s *Recommendations for Reducing Cognitive Impairment and Dementia Risk* [116] identify a number of important lifestyle interventions, such as: physical activity, tobacco cessation, nutrition, interventions for alcohol use disorders, cognition, social functioning, weight management, hypertension management, diabetes management. The strongest recommendations cover areas such as physical activity, tobacco cessation, nutrition, hypertension management and diabetes management. As in the review of the nICP

measurement study in glaucoma patients [9], the potential of yoga exercises must also be considered when looking at the prospects of NTG treatment through the prism of CA and brain health. Although the number of headlines linking yoga and brain health in particular is relatively small, the results suggest that yoga also has a positive impact on brain health. A literature review published in 2015 suggests that yoga promotes activation of the brain's alpha, beta and theta waves, which is associated with improvements in cognition, memory, mood and anxiety; alternate nostril breathing (pranayama) has been found to activate the contralateral hemisphere of the brain, thus providing neurocognitive benefits, with an increase in interhemispheric coherence and symmetry [122]. Another study demonstrates that yoga and aerobic exercise can reduce some of the symptoms of multiple sclerosis, along with such associated factors as the cost and duration of treatment [123]. Gothe et al. conclude in their study that yoga behavioural interventions may be promising to mitigate age–related and neurodegenerative decline [124]. Yoga as a creative lifestyle intervention is a promising tool to improve motor and imitation skills in children with autism spectrum disorder (ASD) [125]. Findings from a meta–analysis of studies published in 2019 suggest that yoga practice may have an effect on functional connectivity of the DMN, activity of the dorsolateral prefrontal cortex during cognitive tasks, and the structure of the hippocampus and the prefrontal cortex, areas of the brain that show significant age–related changes, and may therefore be promising for mitigating age–related and neurodegenerative decline [126]. Acabchuk et al. in a meta–analysis published in 2021 reviewed the impact of yoga and mindfulness–based behavioural interventions on the development of mild head injuries. The authors concluded that the results provided promising evidence that meditation, yoga and mindfulness–based interventions were associated with statistically significant but modest improvements in symptoms, particularly fatigue, depression and quality of life, compared to controls [127]. Another meta–analysis concluded that yoga may be associated with less activation of the amygdala and fewer negative feelings in response to emotionally distressing images; the use of yoga in the clinical management of certain neurological and psychosocial conditions may benefit patients due to its potential neuroplastic effects [128].

In summary, further studies on the impact of yoga exercises are needed to assess the role of yoga in the treatment of glaucoma (and in particular NTG), and these should be tailored according to the subject group. On the one hand, taking into account the risks of certain exercises (e.g. upside down) for GL patients (especially HTG, due to a possible increase in IOP), on the other hand, assessing the impact of the exercises on brain health.

2.3 The human ophthalmic artery as a sensor for non–invasive intracranial pressure monitoring: numerical modelling and *in vivo* pilot study

The aim of this study was to investigate, in a small number of participants, the possibility of nICP (ICPnon–inv) continuous monitoring (up to 1 h) with the perspective of monitoring conscious patients, including GL; additionally introducing

the concept of OA as a pressure sensor. The ICP and IOP values change over the course of the day, influenced by circadian variations, and short–term measurements of these pressures at only a limited time may fail to provide sufficient information. The review only discusses the key points in this respect. Author contributions: formal analysis and writing of the initial draft in discussion with the other co–authors; additional conclusions and recommendations for new biomarkers from a holistic point of view.

Results

An individual linear calibration equation was used for each patient to obtain the ICP values in pressure units, which were then compared with the ICP values. After the removal of TCD signal artefacts, 1928 pairs of data were obtained for the final comparison. The overall mean and SD of the measured differences between the pairs of data is 0.086 ± 1.34 mmHg. Figure 22 shows a plot of the 223 pairs of data values for the first patient (No. 1). A 60 s moving average filter was used to smooth both readings. The maximum difference between the paired data points was 1.61 mmHg. The differences between the pairs of data points measured in all 6 patients are shown in Figure 23. The extremes of the differences are –3.94 and 4.68 mmHg, and 95% of the observations fall in the range of –2.55 to 2.72 mmHg.

Regression analysis showed a strong positive correlation (r = 0.94) between the data from the two–depth TCD and the Codman ICP monitor (Figure 24). The linear equation $y = 0.94x + 0.84$ indicates that OA can be used as a linear pressure sensor with a bias (systematic error) of 0.84 mmHg over the ICP range studied.

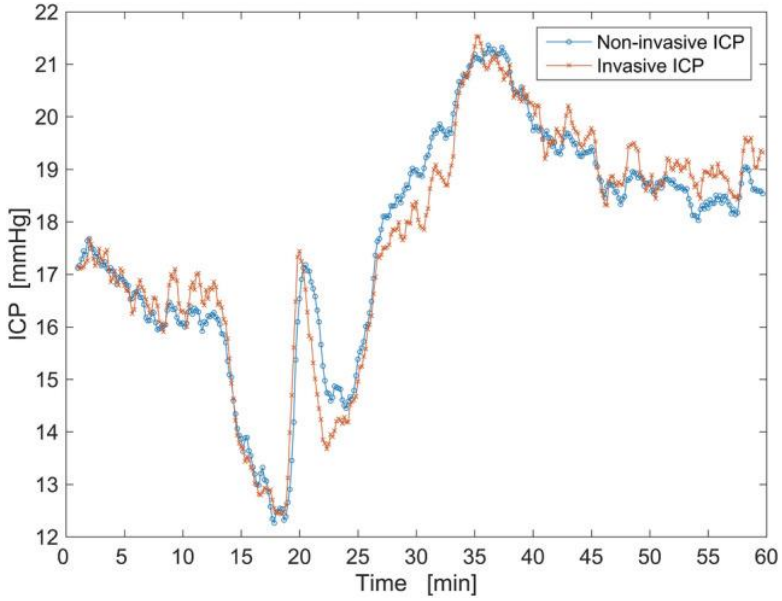


Figure 12. Example of paired ICPinv and ICPnon–inv data for patient #1 (adapt. from [11])

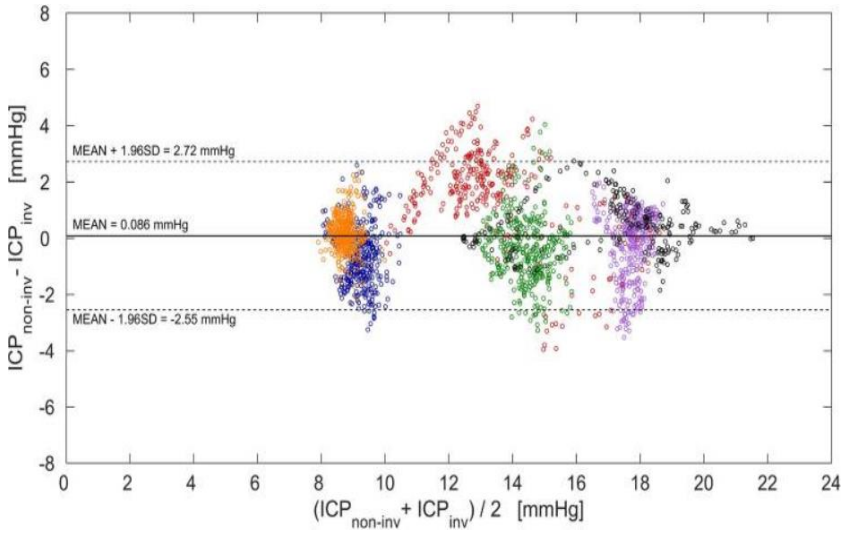


Figure 13. Bland–Altman plot of the distribution of the difference between data pairs (over the pressure range); data from 6 patients separated by 6 colours: black #1, purple #2, blue #3, red #4, orange #5, green #6. The solid horizontal line shows the overall mean of the differences, and the two dashed lines show the standard deviation (SD) of ± 1.96 (adapted from [11])

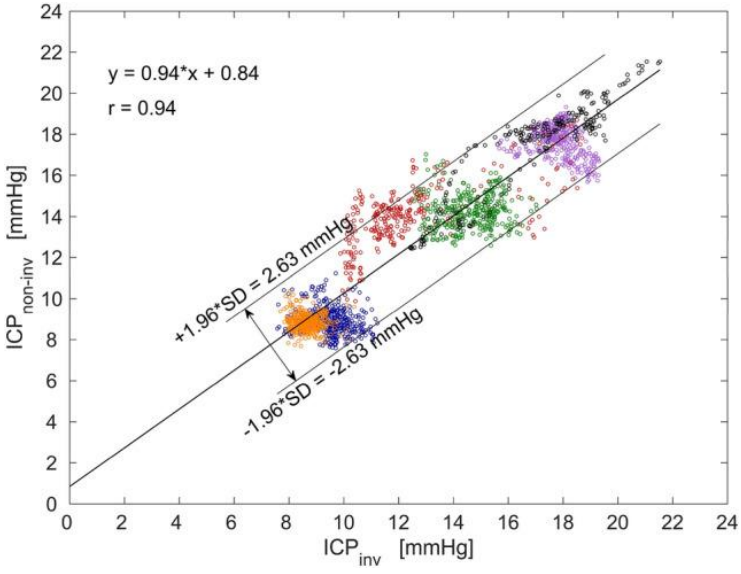


Figure 14. Linear regression plot of all data points. The r = 0.94 indicates that there is a strong positive relationship between ICPnon–inv and ICPinv. Patient data are separated by 6 colours: black #1, purple #2, blue #3, red #4, orange #5 green #6 (adapted from [11])

2.4 Can treatment of normal–pressure glaucoma cause normal–pressure glaucoma? A narrative review of current knowledge

The aim of this article is to narratively review the published literature on the possible association between the treatment of NPH and the development of NTG, and to highlight the need for neuro–ophthalmological follow–up in patients with NPH treated with bypass surgery. Author contributions: analysis of a subset of the selected articles, in discussion with the co–authors; additional findings and recommendations of new biomarkers from a holistic point of view.

Results

The hypothesis of an association between the treatment of NPH with a shunt to reduce ICP and the development of NTG was confirmed in all retrospective studies, case reports and review articles reviewed. The results imply the idea that a safe lower limit of ICP should be maintained in neurological patients (especially in NTG patients treated with shunt). If so, the paradigm of a safe upper ICP limit (as recommended in neurosurgery for ICP < 20 mmHg or ICP < 22 mmHg, and in neurology for ICP < 14.7 mmHg [12]) should be modified to the paradigm of a safe ICP range in neurology and ophthalmology to prevent the progression of NTG.

The measurement of IOP, although indirect, is non–invasive and easily realised by using an applanation tonometer. In contrast, the measurement of ICP is usually difficult because invasive neurosurgical procedures are required to obtain a reliable ICP value. nICP measurement would allow better management of postoperative shunt–treated patients and would stimulate future studies looking for safe lower ICP or upper $\Delta P \times t$ thresholds. Methods for non–invasive ICP assessment are proposed. Only one study of GL patients (to date) was identified that measured nICP in two–depth TCD [56]; the accuracy, precision, diagnostic sensitivity and specificity of this non–invasive ICP technology have been independently tested in different groups of neurological patients; future technologies for measuring nICP in two–depth TCDs should allow for the search for safe lower ICP thresholds that allow the treatment of NPH with no or minimal risk of NTG development and introduce the paradigm of a safe ICP range into clinical practice [12].

Although too low an ICP influences the development of GL, there are emerging publications showing that an additional physiological mechanism has started to emerge as a factor that may influence the development of GL, namely CA, which is a trend that supports the hypothesis tested in our study [12].

3. CONCLUSIONS

1. In both high tension glaucoma (HTG) and normal tension glaucoma (NTG) patients, a statistically significantly ($p < 0.05$) lower than normal (of healthy subjects, HS) intracranial pressure (lowICP), especially combined with a higher than normal intraocular pressure (high IOP), signals an abnormal IOP−ICP pressure difference that could lead to the development of an Lamina Cribrosa (LC) deformation, which is one of the main mechanical causes of primary open–angle glaucoma (especially HTG). Therefore, lowICP could be considered as an additional glaucoma biophysical biomarker (No. 1) signalling the presence of glaucoma (especially HTG) or the risk of developing it. This indirect, non–invasive identification of LC deformity (or the risk of it) would allow to assess the need for physiotherapeutic ocular procedures and targeted yoga exercises and their potential for correction LC shape after deformation or even for treating glaucoma. It is therefore appropriate to include nICP measurement into the protocol for glaucoma diagnosis (especially preventive), thus adding value to the (especially early) diagnosis.

2. Cerebral blood flow autoregulation (CA) is impaired (detCA) in normal tension glaucoma (NTG) patients statistically significantly ($p < 0.05$) if compared to CA in healthy subjects (HS), whereas CA in patients with high tension glaucoma (HTG) was statistically insignificantly different from CA in HS. Therefore, detCA can be considered as an additional glaucoma biophysical biomarker (No. 2) signalling the presence of normal tension glaucoma or the risk of its development. detCA identification would allow to assess the need for CA normalization to manage glaucoma (especially, NTG) development, and would offer patients solutions based on a holistic approach to brain health, such as lifestyle interventions recommended by the *World Health Organisation* and targeted yoga techniques. Such solutions are also relevant for the normalisation of ICP, as lowICP was also found in NTG cases. It is therefore appropriate to include nCA measurement in the protocol for glaucoma diagnostics (especially preventive), thus adding value to the (especially early) diagnosis.

3. The association between normal intracranial pressure hydrocephalus (NPH) treatment by shunting and the risk of glaucoma was established; that fact implies the idea that, in NPH patients undergoing bypass surgery, it is necessary: to use a safe ICP range instead of a safe upper value of ICP (ICP < 20 mmHg in neurosurgery, or ICP < 22 mmHg in neurosurgery, or ICP < 14.7 mmHg in neurology), which also assesses the lower limit of the ICP safe range; and to recommend to patients the regular non–invasive ICP measurements and ophthalmic examinations to manage the risk of glaucoma in the presence of a nICP below the lower limit of the range. In addition, it is proposed to include the above–mentioned potential glaucoma biomarkers lowICP and detCA into the NPH treatment protocol. Similar to lowICP and detCA, comparable types of solutions based on a holistic approach to brain health can be offered to patients.

4. We have been able to demonstrate the association between glaucoma diagnosis and mechanical factors lowICP and detCA by using relatively portable, mobile and inexpensive, reasonably accurate (error probability $p < 5\%$) and efficient non–invasive equipment and methods, thereby formulating a paradigm refinement:

4.1. The current glaucoma paradigm: high IOP is a biophysical biomarker of high tension glaucoma; HTG is a disease influenced by a single pressure (IOP), reasons of NTG are unclear. The revised glaucoma paradigm: highIOP is a biophysical biomarker for high tension glaucoma; lowICP is a biophysical biomarker for high tension glaucoma and normal tension glaucoma; detCA is a biophysical biomarker for normal tension pressure glaucoma; HTG is a disease affected by two pressures (IOP, ICP); NTG is a disease affected by three pressures (IOP, ICP, CA);

4.2. The current paradigm for shunt treatment of normal pressure hydrocephalus (NPH): an ICP value below the upper limit is safe; the revised paradigm for shunt treatment of NPH: too low ICP value is unsafe because it may lead to a risk of glaucoma; there is a safe ICP range within which ICP maintenance is necessary to manage the risk of glaucoma.

Ideas suggested for further research

1. A study on the impact of the new proposed biomarkers lowICP and detCA on glaucoma, testing for a reverse cause–effect relationship; i.e., measuring of nICP and nCA to check for possible lowICP and detCA in patients complaining of visual disturbances who have not yet been tested for glaucoma; and only then measuring of IOP and performing an ophthalmological examination; thus aiming to identify the risk of GL at an early diagnostic stage, even in the absence of overt signs of GL measured by the usual methods included in GL diagnostic protocols.

2. nICP and nCA measurements/monitoring studies in glaucoma patients, collecting as many additional patient data and parameters as possible, in order to search for all possible cause–effect relationships (which may be missed by human) in the next step, by using artificial intelligence tools.

3. Studies on the effect of physiotherapy on the treatment of HTG by means of LC deformation restoration; studies on the effect of yoga exercises to normalise IOP and ICP; to assess their influence on nIOP and nICP and on the course of glaucoma already developing or on the risk of possible GL.

4. Studies on the effect of WHO recommended physical activity and other lifestyle interventions (to improve brain health and possibly also CA), yoga exercises; to assess the impact on nCA and nICP and on the course of or the risk of preexisting or developing GL.

5. Studies of nICP and nCA measurements in patients with NPH treated with bypass surgery (shunting) who are at risk of glaucoma, to assess their impact on the course of or the risk of developing GL.

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CURRICULUM VITAE

Paulius Lučinskas, paulius.lucinskas@gmail.com

Išsilavinimas

2015–2022 Doktorantas, Kauno technologijos universitetas
1997 Magistras, Kauno technologijos universitetas
1991 Patentų inžinierius (patentologas), Lietuvos informacijos institutas
1991 Elektros inžinierius, Kauno technologijos universitetas

Darbo patirtis

2003–dabar Partneris vadybai, komunikacijai ir ledlaužystei, Amiagus Group
2017–2021 Inžinierius, UAB „Verdigo“
2015 Kosmoso terminų redaktorius (Andy Weir "The Martian" bestselerio vertimo į lietuvių k. 1–jo leidimo redakcija), leidykla „Obuolys“
2013–2014 Mentorius, Saulėtekio slėnis
2013 Mentorius, Žinių ekonomikos forumas
2012 Vertėjas (Lietuvių kilmės kosmonauto A. Jeliseevo aka Kuraičio prisiminimų knygos vertimas į lietuvių k.), leidykla „Aviacijos pasaulis“
2010–2012 Portalo administratorius, Tarptautinės kosmoso konferencijos „SEMWO: Space Economy in the Multipolar World“ koprodiuseris ir turinio architektas, Lietuvos aerokosmoso asociacija

1992–2010 Įvairios profesijos ir veiklos: vadyba, radijo laidos, verslas, vertėjavimas, prodiusavimas, dėstymas, moksliniai tyrimai, internetiniai projektai, rašymas

Licencijos ir sertifikatai

2022 Early Health Technology Assessment, Levels A–B, EIT Health RIS Academy
2022 HelloAI Advanced RIS, Health Venture LabHealth Venture Lab
2021 HelloAI RIS Online, Artificial Intelligence Online Training, GE Healthcare
2017 Google Analytics
2017 Google AdWords

Interesų sferos

Mokymasis visą gyvenimą, kelionės, vairavimas, buriavimas, aviacija ir kosmosas, klasikinė muzika, Joga ir Qi–gong, menai, muzikavimas, kalbos, web technologijos, dirbtinis intelektas, statistika, matematika, filosofija; r@šymas.

STRAIPSNIŲ IR MOKSLINIŲ KONFERENCIJŲ SĄRAŠAS

Straipsniai disertacijos tema

1. Deimantavicius M, Hamarat Y, **Lucinskas P**, Zakelis R, Bartusis L, Siaudvytyte L, Janulevicienė I, Ragauskas A. Medicina (Kaunas). 2020 Nov 30;56(12):664. doi: 10.3390/medicina56120664.Prospective Clinical Study of Non–Invasive Intracranial Pressure Measurements in Open–Angle Glaucoma Patients and Healthy Subjects.

2. Hamarat Y, Deimantavicius M, Dambrauskas V, Labunskas V, Putnynaite V, **Lucinskas P**, Siaudvytyte L, Simiene E, Stoskuviene A, Januleviciene I, Petkus V, Ragauskas A. Prospective Pilot Clinical Study of Noninvasive Cerebrovascular Autoregulation Monitoring in Open–Angle Glaucoma Patients and Healthy Subjects. Transl Vis Sci Technol. 2022 Feb 1;11(2):17. doi: 10.1167/tvst.11.2.17.

3. **Lucinskas P**, Deimantavicius M, Bartusis L, Zakelis R, Misiulis E, Dziugys A, Hamarat Y. Human ophthalmic artery as a sensor for non–invasive intracranial pressure monitoring: numerical modeling and in vivo pilot study. Sci Rep. 2021 Feb 26;11(1):4736. doi: 10.1038/s41598–021–83777–x.

4. Hamarat Y, Bartusis L, Deimantavicius M, **Lucinskas P**, Siaudvytyte L, Zakelis R, Harris A, Mathew S, Siesky B, Janulevicienė I, Ragauskas A. Can the Treatment of Normal–Pressure Hydrocephalus Induce Normal–Tension Glaucoma? A Narrative Review of a Current Knowledge. Medicina (Kaunas). 2021 Mar 3;57(3):234. doi: 10.3390/medicina57030234.

Pranešimai mokslinėse konferencijose
(kartu su bendraautoriais)

1. 22–th Meeting of European Society of Neurosonology, 19–21 May 2017, Berlin, Germany; Is Non–invasive continuous monitoring of intracranial pressure absolute value possible?

2. 23rd Meeting of The European Society of Neurosonology and Cerebral Hemodynamics, 13–16 April 2018, Prague, Czech Republic; Comparison of invasive and non–invasive intracranial pressure monitoring

3. ICP 2019 Conference, 08–11 October 2019, Leuven Belgium; 1) Cerebrovascular autoregulation in glaucoma patients 2) Optimal CPP targeted severe TBI patients' treatment: single center study

4. XXIV World Congress of Neurology (WCN 2019) 27–31 October 2019, Dubai, UAE; Glaucoma and Cerebral Blood Flow Autoregulation: Pilot Study

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Prospective Clinical Study of Non-Invasive Intracranial Pressure Measurements in Open-Angle Glaucoma Patients and Healthy Subjects

Mantas Deimantavicius [1], Yasin Hamarat [1,*], Paulius Lucinskas [1], Rolandas Zakelis [1], Laimonas Bartusis [1], Lina Siaudvytyte [2], Ingrida Janulevicienė [2] and Arminas Ragauskas [1]

1 Health Telematics Science Institute, Kaunas University of Technology, 51423 Kaunas, Lithuania; mantas.deimantavicius@ktu.lt (M.D.); paulius.lucinskas@ktu.lt (P.L.); rolandas.zakelis@ktu.lt (R.Z.); laimonas.bartusis@ktu.lt (L.B.); telematics@ktu.lt (A.R.)

2 Eye Clinic, Lithuanian University of Health Sciences, 50161 Kaunas, Lithuania; lynciuke@gmail.com (L.S.); ingrida.januleviciene@kaunoklinikos.lt (I.J.)

* Correspondence: yasin.hamarat@ktu.lt; Tel.: +370-623-19702

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Abstract: *Background and Objective:* Glaucoma is a progressive optic neuropathy in which the optic nerve is damaged. The optic nerve is exposed not only to intraocular pressure (IOP) in the eye, but also to intracranial pressure (ICP), as it is surrounded by cerebrospinal fluid in the subarachnoid space. Here, we analyse ICP differences between patients with glaucoma and healthy subjects (HSs). *Materials and Methods:* Ninety-five patients with normal-tension glaucoma (NTG), 60 patients with high-tension glaucoma (HTG), and 62 HSs were included in the prospective clinical study, and ICP was measured non-invasively by two-depth transcranial Doppler (TCD). *Results:* The mean ICP of NTG patients (9.42 ± 2.83 mmHg) was significantly lower than that of HSs (10.73 ± 2.16 mmHg) ($p = 0.007$). The mean ICP of HTG patients (8.11 ± 2.68 mmHg) was significantly lower than that of NTG patients (9.42 ± 2.83 mmHg) ($p = 0.008$) and significantly lower than that of HSs (10.73 ± 2.16 mmHg) ($p < 0.001$). *Conclusions:* An abnormal ICP value could be one of the many influential factors in the optic nerve degeneration of NTG patients and should be considered as such instead of just being regarded as a "low ICP".

Keywords: primary open angle glaucoma; normal-tension glaucoma; high-tension glaucoma; intracranial pressure; non-invasive ICP measurement

1. Introduction

Glaucoma is a progressive optic neuropathy leading to irreversible vision loss, and is also characterised by structural degeneration of the optic nerve head. The lamina cribrosa (LC), located deep within the optic nerve head [1], is a sieve-like structure in the posterior portion of the sclera that allows optic nerve fibres to exit from the eye [2,3]. The LC plays an important role as a barrier between intraocular pressure (IOP) and intracranial pressure (ICP) [4,5]. Elevated IOP was formerly considered to be the main risk factor in the development of glaucoma, however, elevated IOP is not always present in all forms of glaucoma [5,6]. Primary open-angle glaucoma, which is the most common type of glaucoma worldwide, can be clinically classified into two subgroups: high-tension glaucoma (HTG), in which elevated IOP plays a major role, and normal-tension glaucoma (NTG), in which IOP is within the normal range [7]. Three studies where direct measurements of ICP were performed have demonstrated that ICP is significantly lower in NTG patients than in HTG patients or healthy subjects (HSs) [6,8–10], suggesting that ICP has an impact on glaucoma [11,12]. However, two studies have contradicted this idea and reported no significant differences in ICP between NTG patients and healthy

controls [8,13], suggesting that the ICP regulatory system is not the major component of the NTG pathophysiology [13].

ICP can be monitored in a limited group of patients due to the invasive nature of the measurement. However, a non-invasive measurement method of ICP which has clinically acceptable accuracy, precision, and diagnostic reliability can overcome this limitation [14–16] and can be applied to a wider range of patient groups. The method is based on the principles of a non-invasive arterial blood pressure measurement and uses two depth transcranial Doppler (TCD) ultrasonography to assess blood flow velocity of the ophthalmic artery (OA) during a gradual externally applied pressure (Pe) over a closed eyelid that is transmitted to the eye and orbital (peri-ocular) tissues [17,18].

The aim of this prospective clinical study was to assess ICP differences between glaucoma patients (HTG and NTG) and healthy subjects.

2. Materials and Methods

The prospective clinical study was performed at the eye clinic of the Lithuanian University of Health Sciences. The study was approved by the Kaunas Regional Biomedical Research Ethics Committee (No. BE-2-41, date: 2013-09-03), and all participants provided written informed consent, according to the Declaration of Helsinki.

Glaucoma patients (HTG and NTG) and healthy subjects were enrolled in the study. Only one eye per subject was used for ICP measurement. The eye with greater glaucomatous damage was selected in the glaucoma patient, while the eye was selected randomly in healthy subjects. The inclusion criteria were as follows: clinical diagnosis of glaucoma confirmed by an ophthalmologist, characteristic optic nerve head changes present, and visual field loss consistent with glaucoma. A neurologist examined all patients to exclude neurological disorders that could affect ICP. The exclusion criteria were as follows: pregnant or nursing women, patients with uncontrolled systemic diseases and patients with a history of allergy to local anaesthetics, and orbital/ocular trauma or other diseases that could bias study results. Current medical treatment was continued with the exception of oral carbonic anhydrase inhibitors due to their known effects on ICP. In the case of HSs, volunteers with no history of glaucoma or other diseases that could bias the results were included. Details of inclusion, exclusion criteria, and the study population are shown in Table 1.

The non-invasive measurement method of the absolute value of ICP, which does not need an individual patient-specific calibration, is based on the two-depth high-resolution TCD technique for simultaneously measuring blood flow velocity in the intracranial and extracranial segments of the ophthalmic artery (OA) [14]. A 2-MHz ultrasonic transducer is installed into the head frame together with an air-filled toroidal-shaped soft plastic pressure cuff. Due to the nature of non-compressible orbital tissues as well as the segmentation by the dura mater, the externally applied pressure (Pe) via pressure cuff is transmitted to extracranial OA, but not the intracranial OA. The intracranial segment of the OA is compressed by ICP, and the extracranial segment of the OA is compressed by the externally applied pressure. Blood flow parameters, such as flow velocity pulsations in both OA segments, are approximately equal when Pe = ICP. In this study, Pe was gradually increased from 0 to 20 mmHg by 4 mmHg steps. All subjects were in a supine position during the procedure. The duration of the measurement procedure was up to 10 min [17]. IOP was measured with a Goldmann applanation tonometer just before the non-invasive ICP measurement procedure. All examinations were performed at daytime between 8 am and 2 pm.

Statistical analysis was performed using IBM SPSS Statistics software (version 23.0; IBM Corporation, Armonk, NY, USA). All variables were defined by methods of descriptive statistics. The analysis of the quantitative variables included the calculation of the mean value (Mean) and standard deviation (SD). The Kolmogorov–Smirnov test for the testing of data normality distribution was used for the analysis of all three groups: HTG, NTG, and HSs. The one-way ANOVA test and Tukey multiple comparisons test were performed between subject groups.

Table 1. Details of inclusion and exclusion criteria according to the study group.

Group	Identified	Excluded	Included
NTG	100 patients: NTG confirmed by a glaucoma specialist. Diurnal IOP lower than 21 mmHg before and during treatment.	Five patients excluded due to a lack of willingness.	95 patients
HTG	100 patients: HTG confirmed by a glaucoma specialist. Diurnal IOP higher than 21 mmHg before and during treatment.	40 patients excluded: 17 patients did not want to participate in the study; 8 patients changed their telephone number or were not reachable; 9 patients had an artefact in ICP measurement; 4 patients had trabeculectomy; 1 patient underwent cataract surgery; 1 patient died.	60 patients
HSs	65 subjects: age-matched healthy adults with no history of glaucoma or other diseases that could bias the results.	Three subjects had an artefact in ICP measurement.	62 subjects

NTG: normal-tension glaucoma patients; HTG: high-tension glaucoma patients; HSs: healthy subjects; IOP: intraocular pressure; ICP: intracranial pressure.

3. Results

Two-hundred-seventeen subjects, of which 95 were patients with NTG, 60 were patients with HTG, and 62 were HSs, were included in the statistical analysis of this study, after the exclusion criteria were applied. Demographic data and medication of the subjects are depicted in Table 2. NTG patients had significantly ($p < 0.05$) lower IOP compared to HTG patients (Figure 1). HSs had significantly ($p < 0.05$) lower IOP compared to patients with glaucoma (Figure 1).

Table 2. Composition of the study groups.

Group	Age (Mean ± SD), Years	Gender, Female, %	Glaucoma Surgery	Glaucoma Medications, *N*	Systemic Medications, *N*
NTG	57.52 ± 10.88	79	No	β blockers, 23 Pg analogues, 54 CAIs, 14 α2 agonists, 2	Diuretics, 8 β blockers, 23 ACE inhibitor, 25 ARBs, 4 Others, 38
HTG	57.47 ± 10.90	54	No	β blockers, 13 Pg analogues, 17 CAIs, 10 α2 agonists, 4	Diuretics, 8 β blockers, 14 ACE inhibitor, 17 ARBs, 4 Others, 22
HS	57.39 ± 10.62	60	No	β blockers, 0 Pg analogues, 0 CAIs, 0 α2 agonists, 0	Diuretics, 2 β blockers, 10 ACE inhibitor, 6 ARBs, 1 Others, 14

NTG: normal-tension glaucoma patients; HTG: high-tension glaucoma patients; HSs: healthy subjects; *SD*: standard deviation; *N*: number of subjects; CAIs: carbonic anhydrase inhibitors; ACE: angiotensin converting enzyme; ARBs: angiotensin II receptor blockers.

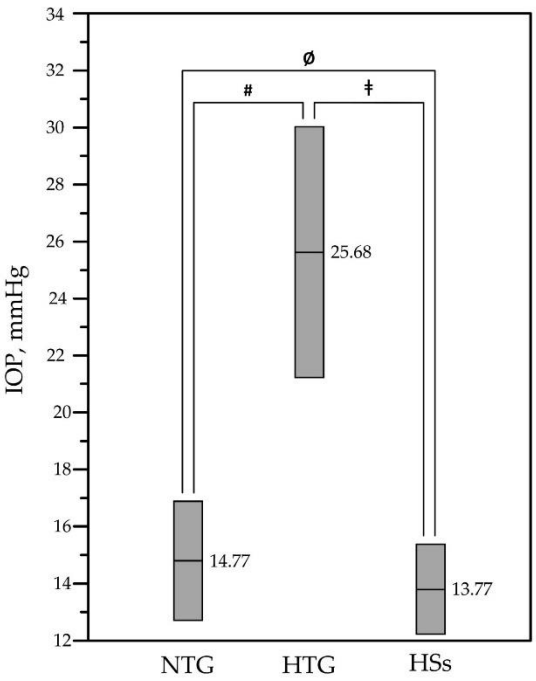

Figure 1. Mean IOP values with standard deviation for NTG, HTG, and HSs. NTG: normal-tension glaucoma patients; HTG: high-tension glaucoma patients; HSs: healthy subjects. Ø—the difference is statistically significant ($p < 0.05$) comparing the means of the IOP data of NTG patients and HSs. #—the difference is statistically significant ($p < 0.05$) comparing the means of the IOP data of NTG patients and HTG patients. ǂ—the difference is statistically significant ($p < 0.05$) comparing the means of the IOP data of HTG patients and HSs.

The Kolmogorov–Smirnov test for the testing of data normality distribution was used for all three groups: NTG, HTG, and HSs. The mean ICP values and tests of data normality are presented in Table 3.

Table 3. Results of the ICP values and tests of data normality.

Group	ICP (Mean ± SD) mmHg	95% CI of the Mean	Med	Min	Max	K–S Test Value	*df*	*p*-Value	Skewness (SE)	Kurtosis (SE)
NTG $N = 95$	9.42 ± 2.83	8.84–10.00	9.25	3.21	15.79	0.05	95	0.200	−0.02 (0.25)	−0.63 (0.50)
HTG $N = 60$	8.11 ± 2.68	7.42–8.80	8.08	3.37	15.17	0.06	60	0.200	0.49 (0.31)	−0.27 (0.61)
HSs $N = 62$	10.73 ± 2.16	10.18–11.28	10.62	7.26	15.17	0.09	62	0.200	−0.29 (0.30)	−0.89 (0.60)

NTG: normal-tension glaucoma patients; HTG: high-tension glaucoma patients; HSs: healthy subjects; *SD*: standard deviation; CI: confidence interval; Med: median; K–S test: Kolmogorov–Smirnov test; *df*: degrees of freedom; *SE*: standard error.

Data did not deviate significantly from the normal distribution, so for the comparison of three independent samples, one-way ANOVA-test was used. Levene's test for the homogeneity of variances was used. The assumption of equal variance was not rejected (Levene statistic value = 2.343, $p = 0.1$). The average ICP values were found to be different across the groups ($F(2.214) = 15.315$, $p < 0.001$).

Tukey multiple comparisons performed at the 0.05 significance level found that the mean ICP of NTG patients (9.42 ± 2.83 mmHg) was significantly lower than that of HSs (10.73 ± 2.16 mmHg) ($p = 0.007$). The mean ICP of HTG patients (8.11 ± 2.68 mmHg) was significantly lower than that of NTG patients (9.42 ± 2.83 mmHg) ($p = 0.008$) and significantly lower than that of HSs (10.73 ± 2.16 mmHg) ($p < 0.001$). Results are presented in Figure 2.

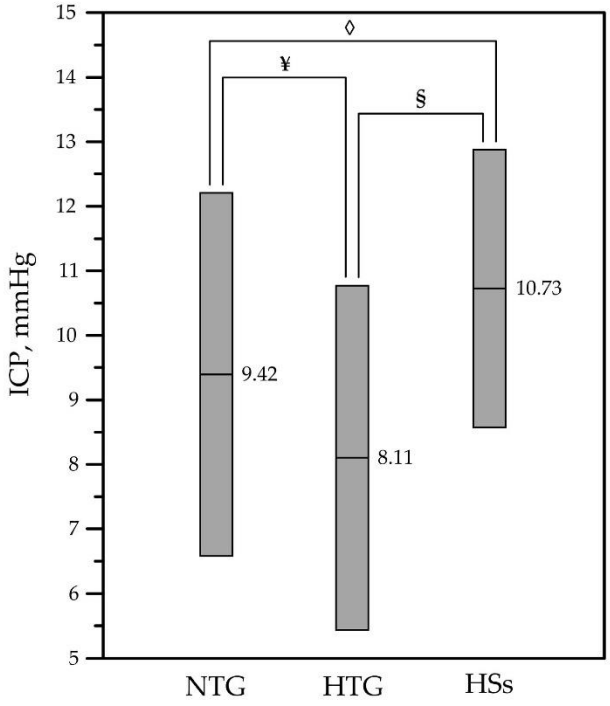

Figure 2. Mean ICP values with standard deviation for NTG, HTG, and HSs. NTG: normal-tension glaucoma patients; HTG: high-tension glaucoma patients; HSs: healthy subjects. ◊—the difference is statistically significant ($p = 0.007$) comparing the means of the ICP data of NTG patients and HSs. ¥—the difference is statistically significant ($p = 0.008$) comparing the means of the ICP data of NTG patients and HTG patients. §—the difference is statistically significant ($p < 0.001$) comparing the means of the ICP data of HTG patients and HSs.

4. Discussion

Although the potential role of low ICP in the pathogenesis of glaucomatous optic neuropathy was described in the late 1970s [19], the underlying mechanism has remained elusive. Some animal studies have been performed to clarify the association between the cerebrospinal fluid (CSF) pressure and glaucoma [20,21]. A limited number of clinical studies have identified lower CSF pressure in patients with NTG compared to individuals without glaucoma [9,22]. A large number of clinical trials are not available yet due to the invasive nature of CSF pressure measurements. The standard clinical procedure to measure ICP is either to use a lumbar puncture technique or to insert a transducer inside the skull. Thus, in some studies of glaucoma patients, ICP was measured not behind the sieve plate but in the spine by means of lumbar puncture [8,9,22,23]. In this study, we have measured ICP non-invasively closer to lamina cribrosa, and this method allows us to distinguish the pressure in both the intracranial and optic nerve subarachnoid spaces.

In this prospective clinical study that included healthy subjects and patients with glaucoma (NTG and HTG), the mean ICP in HTG patients was significantly lower than in NTG patients and in HSs, while the mean ICP in NTG patients was significantly lower than in HSs. Using the non-invasive method to measure ICP, we calculated the mean ICP value in the NTG patients as being similar to values reported in previous studies [9,22]. In a previous pilot study, the same non-invasive device showed similar mean ICP values for HTG patients and for HSs [24] as those reported in this study. In contrast, the mean ICP of the current study for NTG patients was not similar to the previous pilot study [24]. Furthermore, in our study, we found a large variability in ICP, ranging from 3.21 to 15.79 mmHg in the patients with NTG, 3.37 to 15.17 mmHg in the patients with HTG, and 7.2 to 15.17 mmHg in the case of HSs. The ICP begins to decline progressively after the age of 50 years, with a mean ICP of 10.7 ± 2.6 mmHg at age 60–64 years [25], which is similar to our finding, a mean ICP of 10.73 ± 2.16 mmHg in the case of HSs with a mean age 57.39 ± 10.62 years.

The underlying reason for NTG remains somewhat unclear. A significant percentage of NTG patients have a family history of glaucoma [26], yet NTG is considered a multifactorial disease, and vascular dysregulation could be the key factor in the disease pathway [26]. There is an ongoing debate about disturbed CSF dynamics in the NTG pathway. Some studies have reported increased optic nerve sheath diameters in patients with NTG [23,27], which contradicts the idea of decreased ICP in NTG patients. The conflict might be explained by higher tissue elasticity in such patients and compartmentation of the subarachnoid space by means of disturbed CSF flow [23].

Our prospective clinical study is contradictory to a result obtained in an Asian and in an American population, where the lumbar CSF pressure measurements were significantly lower in NTG patients than in HTG patients [6,9]. Our findings also contradicted two other studies (in Switzerland and in Sweden) where no significant differences in ICP were observed between NTG patients and healthy controls [8,13]. Several reasons could explain the differences between the results obtained in our study and other studies. First, ICP is influenced by body position. The lumbar puncture procedure is generally performed at lateral decubitus position, while non-invasive ICP measurement is taken at the supine position. Second, CSF pressure was measured in-between lumbar vertebrae L3/L4 or L4/L5 in the studies mentioned above, while in our study, it was measured close to the region of interest, the optic nerve. This can influence the measurement result, as a cerebrospinal fluid pathway might not fully communicate because the central nervous system has multiple and rigid subdivisions [26]. The optic nerve compartment syndrome could limit the free flow of CSF [5]. Third, ICP and IOP fluctuate over time, and this makes it difficult to evaluate pressure at a certain time [8,26]. Although the time of measurement is important, we did not compare differences between ICP and IOP in this study. Due to a high number of patients and shortage of staff in the clinic, only one IOP and non-invasive ICP measurement were taken per subject (which took place between 8 am and 2 pm). Next, we used a non-invasive ICP measurement method instead of the invasive lumbar puncture technique, which might represent sample errors yet to be revealed. Also, this study did not include a wash-out period; consequently, hypotensive agents might have affected the ICP value. Also, ICP measurements

could be influenced by blood pressure, body mass index, age, and undetermined neurological and systemic disease in different study groups and ethnicities.

5. Conclusions

Here, we found that NTG patients had significantly lower ICP compared to HSs, while HTG patients had significantly lower ICP than NTG patients and HSs. The abnormal ICP value on lamina cribrosa could be one of the many factors influencing optic nerve degeneration of NTG patients and should be considered as such instead of being regarded separately as just a "low ICP".

Author Contributions: Conceptualization: A.R. and I.J.; methodology: Y.H.; software: M.D.; validation: Y.H., L.B., and L.S.; formal analysis: Y.H. and L.B.; investigation: Y.H.; resources: A.R.; data curation: L.S., R.Z., and L.B.; writing—original draft preparation: M.D., Y.H., and P.L.; writing—review and editing: Y.H., L.B., L.S., I.J., and A.R.; visualization: Y.H. and L.B.; supervision: I.J. and A.R.; funding acquisition: L.S. and I.J. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

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Article

Prospective Pilot Clinical Study of Noninvasive Cerebrovascular Autoregulation Monitoring in Open-Angle Glaucoma Patients and Healthy Subjects

Yasin Hamarat[1], Mantas Deimantavicius[1], Vilius Dambrauskas[1], Vaidas Labunskas[1], Vilma Putnynaite[1], Paulius Lucinskas[1], Lina Siaudvytyte[2], Evelina Simiene[2], Akvile Stoskuviene[2], Ingrida Januleviciene[2], Vytautas Petkus[1], and Arminas Ragauskas[1]

[1] Health Telematics Science Institute, Kaunas University of Technology, Kaunas, Lithuania
[2] Eye Clinic, Lithuanian University of Health Sciences, Kaunas, Lithuania

Correspondence: Yasin Hamarat, Kaunas University of Technology, Health Telematics Science Institute, K. Barsauskas Str. 59-A556, Kaunas LT-51423, Lithuania.
e-mail: yasin.hamarat@ktu.lt

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Purpose: To analyze the cerebrovascular autoregulation (CA) dynamics in patients with normal-tension glaucoma (NTG) and high-tension glaucoma (HTG) as well as healthy subjects using noninvasive ultrasound technologies for the first time.

Methods: The CA status of 10 patients with NTG, 8 patients with HTG, and 10 healthy subjects was assessed, using an innovative noninvasive ultrasonic technique, based on intracranial blood volume slow-wave measurements. Identified in each participant were intraocular pressure, ocular perfusion pressure, and CA-related parameter volumetric reactivity index (VRx), as well as the duration and doses of the longest cerebral autoregulation impairment (LCAI). In addition, we calculated the associations of these parameters with patients' diagnoses.

Results: The VRx value, the LCAI dose, and duration in healthy subjects were significantly lower than in patients with NTG ($P < 0.05$). However, no significant differences were noted in these parameters between healthy subjects and HTG and between NTG and HTG groups.

Conclusions: NTG is associated with the disturbed cerebral blood flow and could be diagnosed by performing noninvasive CA assessments.

Translational Relevance: The VRx monitoring method can be applied to a wider range of patient groups, especially patients with normal-tension glaucoma.

Introduction

Glaucoma is a multifactorial, progressive neurodegenerative disorder that results in optic nerve head damage and visual field loss. Patients with high range intraocular pressure (IOP) can develop glaucoma. However, patients with normal-range IOP can also develop glaucomatous optic neuropathy. Primary open-angle glaucoma is the most common type of glaucoma worldwide and can be clinically classified into two subgroups: high-tension glaucoma (HTG), in which IOP is greater than 21 mm Hg, and normal-tension

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glaucoma (NTG), in which IOP is within the normal range.[1]

The pathogenesis of glaucoma is not fully understood. However, several theories have been put forward such as mechanical and vascular theories to explain the pathogenesis of glaucoma.[2–4] The mechanical theory considers glaucomatous optic neuropathy to be a direct consequence of IOP, which damages the laminar cribrosa and neural axons.[5,6] However, the vascular theory considers glaucomatous optic neuropathy as a consequence of low perfusion pressure of the optic nerve.[3,7] The decreased optic nerve perfusion may result from vascular failure that includes vasospasms, small vessel disease, and autoregulatory dysfunction.[8,9]

However, explanations of NTG are still controversial. Studies believe that glaucoma causes dysfunction of the autoregulation of the ocular blood flow.[10,11] Typically, the ocular blood flow autoregulation is characterized by local vascular constriction or dilation, which makes vascular resistance reciprocally increase or decrease, thereby keeping a relatively constant temperature for ocular and constant pressure for retinal perfusion.[10,11]

Other studies suggest that disturbed ocular blood flow is a major factor associated with the pathogenesis of NTG.[6,12] Disturbance in the autoregulatory pathway may decrease perfusion and lead to ischemic damage of the optic nerve or retinal ganglion cells.[10] Although several methods have been put forward, no single vascular indicator can completely evaluate ocular blood flow.[13]

Vascular dysregulation in glaucoma is one of the results of impaired cerebrovascular autoregulation[14] and probably explains the association between glaucoma and disorders such as vasospasm, endothelial dysfunction, and migraine.[10,14] Retinal circulation mirrors cerebral circulation,[15] and they share similar anatomic, physiologic, and embryologic characteristics.[16] Abnormalities of the retinal arterioles are a useful indicator of systemic and neurodegenerative diseases such as diabetes, hypertension, multiple sclerosis, Alzheimer disease.[17] Thus, blood flow in the retina is autoregulated in the same way as cerebral blood flow—that is, constant blood flow in the eye is maintained in the retina despite changes in the perfusion pressure,[13] but only within certain limits. Moreover, the diameter of the blood vessels in the retina depends on the activity of the neurons in the retina. This process is known as neurovascular interaction.

When the ocular perfusion pressure decreases below a patient-specific lower threshold, the autoregulation of the retina blood flow is impaired. Hypothetically, it may lead to the development of glaucoma. As for the brain, the cerebral vascular system must respond to changes in arterial blood pressure (ABP) or cerebral perfusion pressure (CPP) to maintain stable cerebral blood flow. The mechanism of stabilizing cerebral CPP despite fluctuations in cerebral blood flow is known as cerebrovascular autoregulation. Thus, the blood autoregulation of the central nervous system and that of the eyes is similar, which has inspired a hypothesis that the impairment of eye blood flow in the case of glaucoma is associated with cerebrovascular autoregulation impairment.

Conventional methods for cerebrovascular autoregulation measurement have several limitations (e.g., invasive methods such as surgical access, catheterization, arterial puncture). Several noninvasive methods for cerebrovascular autoregulation monitoring were suggested to overcome these limitations. Transcranial Doppler (TCD) technologies are used to monitor blood flow measurement from the local artery. The mean flow index can provide different information about cerebrovascular autoregulation in patients with strokes, cerebrovascular disease, or traumatic brain injury, depending on the hemisphere.[18] Approximately 10% to 20% of the population are missing the temporal window. Therefore, TCD measurements are impossible for cerebrovascular autoregulation monitoring. In the case of near-infrared spectroscopy (NIRS)–based technologies, regional cerebral oxygen saturation from the external cortex region is used for cerebrovascular autoregulation monitoring.[18] Thus, the main advantage of the volumetric reactivity index (VRx) is the ability to assess cerebrovascular autoregulation more globally, because intracranial blood volume (IBV) changes are measured in both hemispheres, averaging them over the entire acoustic path.[18]

The present prospective study applied noninvasive ultrasound techniques to explore the cerebrovascular autoregulation (CA) dynamics in patients with glaucoma (NTG and HTG) and healthy subjects for the first time.

Methods

This prospective clinical study was conducted at the eye clinic of the Lithuanian University of Health Sciences. The study was approved by Kaunas Regional Biomedical Research Ethics Committee (No. BE-2-41, date: September 3, 2013), and according to the Declaration of Helsinki, written informed consent was obtained from all participants.

Patients with glaucoma (HTG and NTG) and healthy subjects were enrolled in the study. The inclusion criteria were as follows: an ophthalmologist-

confirmed clinical diagnosis of glaucoma, the presence of changes in the optic nerve head, and visual field loss consistent with glaucoma. The exclusion criteria were pregnant patients or nursing mothers, patients with uncontrolled systemic diseases, and those with a history of allergy to local anesthetics, orbital/ocular trauma, or other diseases that could bias the study results. Healthy subjects included age-matched volunteers with no history of glaucoma or other diseases that could bias the results.

Thickness of the retinal nerve fiber layer (RNFL) was analyzed using confocal scanning laser ophthalmoscopy (Heidelberg retinal tomography, HRT3, software version 3.1; Heidelberg Engineering, Heidelberg, Germany). Standard automated perimetry was conducted using the Humphrey 24-2 Swedish interactive thresholding algorithm perimeter (Humphrey Standard Perimetry; Carl Zeiss Meditec, 07745 Jena, Germany). Visual field testing was considered unreliable if the fixation losses exceeded 20% and if the false-negative or false-positive errors exceeded 33%. Mean deviation (MD), pattern standard deviation (PSD), and visual field index (VFI) were assessed. Color Doppler imaging (Accuvix, Seoul, Korea) was used for retrobulbar blood flow measurements in the ophthalmic, central retinal, and short posterior ciliary arteries. In each vessel, peak systolic velocity (PSV) and end-diastolic velocity (EDV) were assessed, and resistance index (RI) was calculated (Porcelot's formula: $RI = (PSV - EDV)/PSV$).

The status of cerebrovascular autoregulation was monitored in participants using the innovative noninvasive ultrasonic technique (Vittamed 505 monitor; Boston Neurosciences, Lexington, MA, USA) based on the ultrasonic time-of-flight (TOF) measurement principle, capable of sensing intracranial density changes within the acoustic path, due to IBV fluctuation used as a surrogate of intracranial pressure (or cerebral blood flow) slow changes for cerebrovascular autoregulation assessment.[19–22] A head frame with a pair of ultrasonic transducers (2 MHz), positioned on opposite sides of the head on temporal bones, was used to transmit and receive an ultrasound pulse that crossed the brain parenchyma and cerebral ventricles (Fig. A1). Fluctuation of TOF is inversely proportional to changes in IBV because the ultrasound speed in the blood is greater than in other intracranial components (parenchyma and cerebrospinal fluid). Thus, an increase in blood volume within the acoustic path leads to an increase in the average relative ultrasound speed and decrease in TOF changes, $\Delta IBV(t) \sim 1/TOF(t) \sim -\Delta TOF(t)$. Assuming that slow IBV changes are correlated to slow intracranial pressure changes (or slow cerebral blood flow changes), we use reverse $\Delta TOF(t)$ data for the VRx calculation: $VRx = r(ABPsw(t); IBVsw) = r(ABPsw(t); -\Delta TOF(t))$,[18,23,24] where ABPsw(t) are arterial blood pressure slow waves, and IBVsw(t) are intracranial blood volume slow waves.

$\Delta TOF(t)$ – slow changes of time-of-flight that inversely reflects slow IBV changes; slow waves with period of 0.5 to 2.0 minutes reflect the vasogenic activity of cerebrovascular autoregulation. ICM + software (Cambridge, UK) was used for monitoring data collection and real-time VRx calculation. The ABP monitor (Finapres Nova, Enschede, Netherlands) was employed for this study (Fig. A1). The sampling frequency of TOF data collection was 50 Hz. Two-minute moving time windows of slow IBV(t) and ABP(t) slow waves were used for temporary VRx(t) calculation.[18,23] A band-pass filter as used to extract waves from IBV and ABP data.

The CA monitoring session lasted up to 15 minutes for each subject. All subjects were asked to perform the Valsalva maneuver (up to 15–20 seconds) once per minute to generate repetitive slow waves and physiologic reactions needed for CA assessment.[25] Negative values ($VRx(t) < 0$) correspond to intact CA status, whereas positive values ($VRx(t) > 0$) indicate CA impairment.[18,23]

For each episode of CA impairment, we estimated the duration of the single longest CA impairment event (LCAI) and the LCAI dose. The LCAI duration was calculated using thresholds of $VRx > 0$, which represents the mathematical threshold for CA impairment, in which $VRx > 0.4$, associated with patient outcome (similar thresholds of 0.4–0.5 are also used for other noninvasive CA indexes, such as the mean flow index [transcranial Doppler-based CA measurements][26] and cerebral oximetry index [NIRS-based CA indexes]).[27] The LCAI dose was calculated as the area under the curve of $VRx > 0$. The average VRx, duration of a single LCAI event, and LCAI dose were chosen to evaluate and compare the CA impairment in patients with glaucoma and healthy subjects.

Statistical data analysis was conducted using IBM SPSS (version 23.0; IBM Corporation, Armonk, NY, USA). All variables were defined and summarized using descriptive statistics, presented as the mean values and standard deviations (SDs). The Shapiro–Wilk normality test was used to assess normal distribution. The Mann–Whitney *U* test was used to calculate differences between continuous variables and differences between groups for two independent samples. The Kruskal–Wallis test was used to calculate differences between continuous variables and differences between groups for more than two independent samples.

Results

In this prospective clinical study, the 28 participants were divided into three groups: 10 patients with NTG, 8 patients with HTG, and 10 healthy subjects. Table 1 presents the composition of the study groups. In healthy subjects, the means of RNFL thickness in superior, nasal, inferior, and temporal quadrants were measured as 124.1 ± 13.6, 79.8 ± 12.2, 142.4 ± 13.4, and 76.6 ± 9.0 µm, respectively. In the case of NTG, the means of RNFL thickness in superior, nasal, inferior, and temporal quadrants were 106.9 ± 19.3, 76.9 ± 13.4, 111.0 ± 35.4, and 67.9 ± 12.5 µm, respectively. However, the means of RNFL thickness in superior, nasal, inferior, and temporal quadrants of

Table 1. Basic Parameters of the Study Group

Characteristic	HS	NTG	HTG	χ^2	*df*	*P* Value
Number of subjects	10	10	8	—	—	—
Age, mean ± SD, y	71.1 ± 5.1[b]	67.5 ± 2.3[c]	73.2 ± 2.7[b,c]	**12.899**	**2**	**0.020**
Gender (male), %	20	10	12.5	—	—	—
Body mass index, mean ± SD	27.97 ± 5.01	28.49 ± 5.37	26.93 ± 3.18	0.140	2	0.932
Family members with glaucoma, %	0	40	0	—	—	—
Glaucoma surgery	No	No	No	—	—	—
Illness period, mean ± SD, y	—	4.3 ± 4.98	4.97 ± 5.03	1.361	1	0.243
Glaucoma medications, *n* (%)						
β-Blockers	0 (0)	2 (20)	2 (25)	—	—	—
Pg analogues	0 (0)	7 (70)	5 (62.5)	—	—	—
CAIs, N (%)	0 (0)	4 (40)	3 (37.5)	—	—	—
α2-Agonists	0 (0)	0 (0)	4 (50)	—	—	—
Systemic medications, *n* (%)						
Diuretics	0 (0)	0 (0)	2 (25)	—	—	—
β-Blockers	2 (20)	6 (60)	5 (62.5)	—	—	—
ACE inhibitors	1 (10)	1 (10)	0 (0)	—	—	—
ARBs	1 (10)	1 (10)	0 (0)	—	—	—
Others	8 (80)	9 (90)	4 (50)	—	—	—
Mean ABP, mean ± SD, mm Hg	98.3 ± 5.5	104.7 ± 9.3	97.4 ± 13.7	3.110	2	0.211
IOP, mean ± SD, mm Hg	14.5 ± 2.0[b]	14.2 ± 1.7[c]	18.9 ± 4.8[b,c]	**8.034**	**2**	**0.018**
OPP, mean ± SD, mm Hg	55.9 ± 4.3[a]	60 ± 4.9[a]	52.4 ± 9.9	5.561	2	0.059
RNFL, mean ± SD, µm	106.7 ± 8.0[a,b]	90.8 ± 16.7[a]	77.0 ± 25.1[b]	**9.837**	**2**	**0.007**
Superior RNFL, mean ± SD, µm	124.1 ± 13.6[b]	106.9 ± 19.3	85.1 ± 37.5[b]	**6.527**	**2**	**0.038**
Nasal RNFL, mean ± SD, µm	79.8 ± 12.2	76.9 ± 13.4	63.8 ± 27.4	2.286	2	0.319
Inferior RNFL, mean ± SD, µm	142.4 ± 13.4[a,b]	111.0 ± 35.4[a]	96.1 ± 28.4[b]	**12.406**	**2**	**0.002**
Temporal RNFL, mean ± SD, µm	76.6 ± 9.0	67.9 ± 12.5	59.5 ± 21.3	3.415	2	0.181
Visual field parameters						
MD, mean ± SD, dB	−0.89 ± 0.62[a,b]	−4.37 ± 2.96[a]	−6.76 ± 6.67[b]	**4.921**	**2**	**0.007**
PSD, mean ± SD, dB	1.65 ± 0.35[a]	4.79 ± 2.67[a]	5.60 ± 4.88	**6.793**	**2**	**0.014**
VFI, mean ± SD, %	98.80 ± 0.63[a,b]	90.20 ± 7.89[a]	84.88 ± 17.21[b]	**5.934**	**2**	**0.005**

P value is based on nonparametric Kruskal–Wallis test for more than two independent samples. ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CAI, carbonic anhydrase inhibitors; HS, healthy subjects; OPP, ocular perfusion pressure; Pg, prostaglandin; —, XXX.

[a]Cases of statistically significant ($P < 0.05$) differences between two independent samples based on Mann–Whitney test between HS and NTG.

[b]Cases of statistically significant ($P < 0.05$) differences between two independent samples based on Mann–Whitney test between HS and HTG.

[c]Cases of statistically significant ($P < 0.05$) differences between two independent samples based on Mann–Whitney test between NTG and HTG.

Bold values indicate that $p < 0.05$.

Table 2. Flow Velocities and Resistance Index in the Ophthalmic, Central Retinal, and Short Posterior Ciliary Arteries at Baseline

Characteristic	HS ($n = 10$), Mean ± SD	NTG ($n = 10$), Mean ± SD	HTG ($n = 8$), Mean ± SD	χ^2	*df*	*P* Value
Ophthalmic artery						
Peak systolic velocity, cm/s	34.38 ± 8.51	31.80 ± 8.34	35.53 ± 7.49	0.498	2	0.780
End-diastolic velocity, cm/s	6.83 ± 1.81	8.01 ± 2.43	9.88 ± 4.73	2.860	2	0.239
Resistance index	0.79 ± 0.05	0.75 ± 0.04	0.73 ± 0.06	4.305	2	0.116
Central retinal artery						
Peak systolic velocity, cm/s	9.31 ± 2.28	10.15 ± 2.05	9.89 ± 2.01	0.836	2	0.658
End-diastolic velocity, cm/s	3.33 ± 0.52	3.55 ± 0.84	3.48 ± 0.44	0.594	2	0.743
Resistance index	0.62 ± 0.06	0.64 ± 0.06	0.63 ± 0.07	0.188	2	0.910
Short posterior ciliary arteries						
Peak systolic velocity, cm/s	8.06 ± 1.24	8.84 ± 1.63	8.24 ± 1.92	1.125	2	0.570
End-diastolic velocity, cm/s	4.19 ± 0.92	4.05 ± 0.49	3.87 ± 0.58	0.547	2	0.761
Resistance index	0.47 ± 0.04	0.53 ± 0.07	0.51 ± 0.09	2.430	2	0.297

P value is based on nonparametric Kruskal–Wallis test for more than two independent samples.

Cases of statistically significant ($P < 0.05$) differences between two independent samples based on Mann–Whitney test between HS and NTG.

Cases of statistically significant ($P < 0.05$) differences between two independent samples based on Mann–Whitney test between HS and HTG.

Cases of statistically significant ($P < 0.05$) differences between two independent samples based on Mann–Whitney test between NTG and HTG.

Table 3. Cerebrovascular Autoregulation-Related Parameters

Characteristic	HS ($n = 10$), Mean ± SD	NTG ($n = 10$), Mean ± SD	HTG ($n = 8$), Mean ± SD	χ^2	*df*	*P* Value
VRx, mean ± SD	−0.18 ± 0.22[a]	0.06 ± 0.17[a]	−0.07 ± 0.25	5.362	2	0.068
LCAI duration, mean ± SD, VRx > 0, s	127 ± 66[a]	281 ± 151[a]	231 ± 218	**7.858**	**2**	**0.020**
LCAI duration, mean ± SD, VRx > 0.4, s	13 ± 38[a]	73 ± 59[a]	42 ± 65	**7.156**	**2**	**0.028**
LCAI dose, mean ± SD, s	31 ± 29[a]	107 ± 77[a]	75 ± 85	**8.794**	**2**	**0.012**

P value is based on nonparametric Kruskal–Wallis test for more than two independent samples.

[a]Cases of statistically significant ($P < 0.05$) differences between two independent samples based on Mann–Whitney test between HS and NTG.

Cases of statistically significant ($P < 0.05$) differences between two independent samples based on Mann–Whitney test between HS and HTG.

Cases of statistically significant ($P < 0.05$) differences between two independent samples based on Mann–Whitney test between NTG and HTG.

Bold values indicate that $p < 0.05$.

HTG were 85.1 ± 37.5, 63.8 ± 27.4, 96.1 ± 28.4, and 59.5 ± 21.3 µm, respectively. Statistically significant differences were detected between the three groups, as shown in Table 1. Patients with glaucoma had significantly worse visual field measures (VFI, MD, PSD) compared to healthy subjects.

Table 2 shows the flow velocities and RI in the ophthalmic, central retinal, and short posterior ciliary arteries at baseline. No significant difference was detected in blood flow velocities. The RI in all three vessels did not differ in the three study populations.

Table 3 shows the CA monitoring results. From the Shapiro–Wilk normality test, the CA monitoring data failed to show a normal distribution; therefore, a comparison was made by the Mann–Whitney *U* test. The average VRx was −0.18 ± 0.22 for healthy subjects, 0.06 ± 0.17 for patients with NTG, and −0.07 ± 0.25 for patients with HTG. The VRx value for healthy subjects was significantly lower than that of patients with NTG ($P < 0.05$). No significant differences were noted between the healthy subjects and HTG groups and between the NTG and HTG groups ($P = 0.36$ and

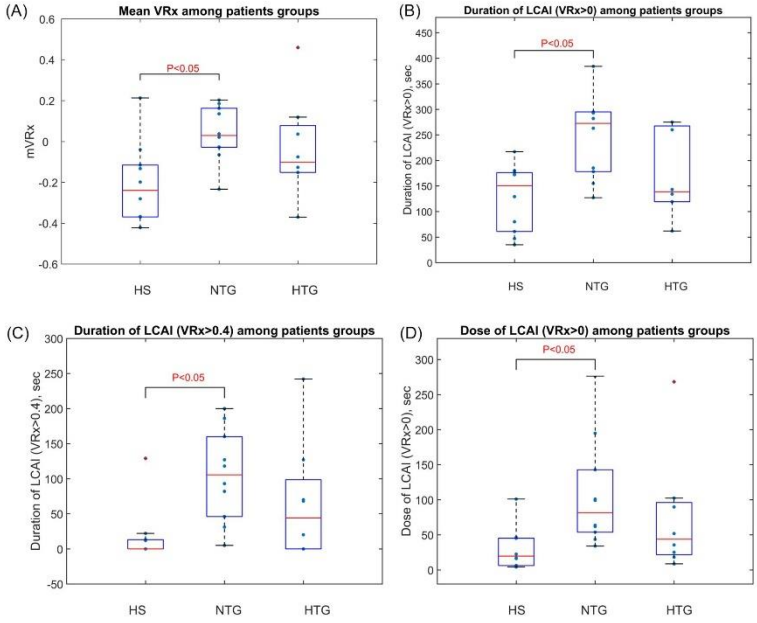

Figure 1. (**A**) Distribution of VRx among the study groups. (**B**) Longest cerebral autoregulation impairment event duration (VRx > 0) for different study groups. (**C**) Longest cerebral autoregulation impairment event duration (VRx > 0.4) for different study groups. (**D**) Longest cerebral autoregulation impairment event dose for different study groups. The longest cerebral autoregulation impairment event dose was calculated as the area under VRx > 0 curve. HS, healthy subjects.

$P = 0.24$, respectively). The VRx distribution among study groups is presented in Figure 1A.

The LCAI duration (VRx > 0) was 127 ± 66 seconds for healthy subjects, 281 ± 151 seconds for patients with NTG, and 231 ± 218 seconds for patients with HTG. The LCAI duration for healthy subjects was significantly lower than that of patients with NTG ($P < 0.05$). However, no significant differences were noted between healthy subjects and patients with HTG and between patients with NTG and HTG ($P = 0.35$ and $P = 0.10$, respectively). The results of the LCAI duration for the study groups are shown in Figure 1B.

The LCAI duration (VRx > 0.4) was 13 ± 38 seconds in healthy subjects, 73 ± 59 seconds in patients with NTG, and 42 ± 65 seconds in patients with HTG. The LCAI duration of healthy subjects was significantly lower than in patients with NTG ($P < 0.05$). However, no significant differences were noted between healthy subjects and patients with HTG and between patients with NTG and HTG ($P = 0.20$ and $P = 0.15$, respectively). The results of the study group's LCAI duration are shown in Figure 1C.

The LCAI dose (VRx > 0) was 31 ± 29 seconds in healthy subjects, 107 ± 77 seconds in patients with NTG and 75 ± 85 seconds in patients with HTG. The LCAI dose of healthy subjects was significantly lower than that of the patients with NTG ($P < 0.05$). However, no significant differences were noted between healthy subjects and patients with HTG and between patients with NTG and HTG ($P = 0.12$ and p =0 .17, respectively). The results of the LCAI dose for different study groups are presented in Figure 1D.

Discussion

In this prospective clinical study, compromised cerebral autoregulation was observed in patients with NTG through CA impairment parameters based on VRx and the duration and doses of LCAI. No statistically significant difference was noted between patients with HTG and healthy subjects. The findings support our hypothesis regarding the association between CA impairments and NTG development, showing that NTG can disturb cerebral blood flow rather than eye pathology.

Other studies also present the hypothesis regarding the role of CA in NTG or glaucoma formation. Tutaj et al.[14] suggested that the compromised CA in patients with glaucoma can be associated with vascular dysregulation. Impaired vascular autoregulation that causes nonconstant blood flow to the retina and optic nerve may contribute to changes in the optic nerve head, thereby provoking glaucoma.

Cerebrovascular disease plays a critical role in the pathogenesis of glaucoma[28] and is more frequent in patients with NTG than in patients with HTG or healthy subjects.[29] Thus, our prospective clinical research provides evidence of cerebrovascular dysfunction in patients with NTG. Recent studies have shown reduced cerebrovascular blood flow velocities[30,31] and increased risk of Alzheimer disease or other dementia in patients with NTG.[32] However, few studies revealed changes in a hemodynamic parameter of the middle cerebral artery in patients with glaucoma.[30,33,34]

Thus, glaucoma progression is associated with decreased cerebral blood flow.[35] Moreover, vascular insufficiency through unstable ocular blood flow leads to retinal ganglion cell loss[36,37] and visual field deficits. Therefore, glaucoma plays an important role in the pathogenesis of glaucomatous optic neuropathy.[38] Treatment based on the increasing systematic blood flow can improve the visual field in some patients with NTG.[39,40] The endothelium is the primary regulator of vascular homeostasis,[41] and it plays a vital role in controlling blood flow.[40,42] Although several studies have shown endothelial dysfunction in patients with NTG,[42–44] direct evidence of local ocular endothelial dysfunction is difficult to establish. Therefore, the link between endothelial dysfunction and progression in patients with NTG is unclear.

Our findings and evidence from other studies discussed above independently confirm the NTG association between cerebral blood flow pathology and disturbed CA. Therefore, a CA assessment test (Valsalva maneuver,[18] cold pressor,[45] squat-stand,[46] etc.) using noninvasive technologies (VRx, TCD, or NIRS) is recommended for personalized identification of glaucoma-related factors and for choosing appropriate treatments for patients with NTG and HTG.

For CA assessment, we have chosen a noninvasive ultrasonic TOF technique capable of deriving CA-related VRx indexes from IBV fluctuation averaged over the ultrasound wave propagation path from the left to right sides of the temporal bones crossing both hemispheres. The ability to provide a more global CA estimation over the entire cranium is the main advantage of the VRx-based CA assessment technique over other noninvasive CA assessment techniques (TCD or NIRS based). The TCD-based technique is based on blood flow measurement in regional cerebral arteries, and the NIRS-based technique measures intracranial blood fluctuations in the cortex only, which is limited to a 2- to 3-cm depth. Moreover, the application of the TCD-based technique is limited due to temporal window failure in 8% to 20% of the subjects.[47] Meanwhile, the TOF technique used in this study can measure IBV fluctuation for all tested subjects. A study that tested this novel noninvasive TOF technique for patients with TBI showed a significant coincidence between noninvasive (VRx) CA and invasive (pressure reactivity index) CA, estimating the significant associations between VRx indexes and outcome of patients with TBI.[18] An additional clinical study of this noninvasive CA technique on cardiac surgery patients with cardiopulmonary bypass showed that duration of CA impairment events more than 5 minutes during surgery is associated with postoperative cognitive deterioration.[15]

Our previous studies also showed that CA impairment events and their duration can be detected using the VRx index at different thresholds: VRx > 0 and VRx > 0.4, a theoretical threshold value separating intact CA (VRx < 0) and impaired CA (VRx > 0). In this study, we obtained the highest statistical significance between healthy subjects and NTG groups when measuring the LCAI duration with a threshold of VRx > 0.4 (Table 3, Fig. 1C). Similar thresholds (0.4–0.5) have also been used for other noninvasive CA indexes (pressure reactivity index, mean flow index, and cerebral oximetry index) to detect CA impairment[26,27,48] in the noisy data and cases with low slow-wave amplitude. The limited number of patients in the groups was the main limitation of this pilot study. Larger numbers of subjects are needed to obtain statistically significant results and test the hypothesis regarding the relationship between glaucoma and CA impairments. Another limitation is the absence of a gold-standard index of CA. The invasive pressure reactivity index requires invasive sensors as it only provides a rough estimate of CA status, and it is used

only for patients with TBI. Our previous prospective clinical studies showed that the VRx index could be used for CA assessment in patients with TBI[18] and patients undergoing cardiac surgery with cardiopulmonary bypass.[23]

Conclusion

In this pilot study, we demonstrated that NTG is associated with disturbed cerebral blood flow, which can be diagnosed by performing noninvasive CA assessments based on VRx monitoring. Further clinical studies are needed to prove this hypothesis.

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Appendix

Figure A1.

Figure A1. The CA monitoring setup includes the noninvasive ultrasonic TOF monitoring device with the head frame, noninvasive blood pressure monitoring device, and a personal computer with "ICM+" software for real-time calculation of CA index (VRx). A head frame bearing a pair of ultrasonic transducers (2 MHz) on either side of the patient's head was positioned to transmit and receive the ultrasound wave.

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Human ophthalmic artery as a sensor for non-invasive intracranial pressure monitoring: numerical modeling and in vivo pilot study

Paulius Lucinskas[1], Mantas Deimantavicius[1], Laimonas Bartusis[1], Rolandas Zakelis[1], Edgaras Misiulis[2], Algis Dziugys[2] & Yasin Hamarat[1]✉

Intracranial pressure (ICP) monitoring is important in managing neurosurgical, neurological, and ophthalmological patients with open-angle glaucoma. Non-invasive two-depth transcranial Doppler (TCD) technique is used in a novel method for ICP snapshot measurement that has been previously investigated prospectively, and the results showed clinically acceptable accuracy and precision. The aim of this study was to investigate possibility of using the ophthalmic artery (OA) as a pressure sensor for continuous ICP monitoring. First, numerical modeling was done to investigate the possibility, and then a pilot clinical study was conducted to compare two-depth TCD-based non-invasive ICP monitoring data with readings from an invasive Codman ICP microsensor from patients with severe traumatic brain injury. The numerical modeling showed that the systematic error of non-invasive ICP monitoring was < 1.0 mmHg after eliminating the intraorbital and blood pressure gradient. In a clinical study, a total of 1928 paired data points were collected, and the extreme data points of measured differences between invasive and non-invasive ICP were − 3.94 and 4.68 mmHg (95% CI − 2.55 to 2.72). The total mean and SD were 0.086 ± 1.34 mmHg, and the correlation coefficient was 0.94. The results show that the OA can be used as a linear natural pressure sensor and that it could potentially be possible to monitor the ICP for up to 1 h without recalibration.

Continuous intracranial pressure (ICP) monitoring is limited due to the invasive nature of some techniques. Nevertheless, the high risk/benefit ratio allows for the usage of invasive ICP monitors in certain groups of patients who could have sudden pathophysiological ICP variation. Such spontaneous ICP changes are common in traumatic brain injury (TBI) patients[1]. Therefore, invasive ICP monitoring is mostly performed in patients with severe TBI (Glasgow Coma Scale score of 3–8)[2]. The gold-standard ICP-monitoring method is considered to be an intraventricular drain connected to an external pressure transducer. Another major technique for continuous ICP monitoring involves intraparenchymal devices, which are not as accurate as intraventricular drains and cannot be recalibrated once inserted[3,4].

ICP monitoring is in demand in many clinical applications, including conscious patients (ophthalmology, neurology, aerospace medicine, etc.). In the case of ophthalmology, glaucoma is the second leading cause of irreversible vision loss worldwide. It affected 76 million people in 2020 and is predicted to reach 111.8 million cases by 2040[5]. Prospective and retrospective studies using lumbar puncture technique have revealed that glaucoma patients have lower ICP than age-matched healthy subjects[6–9], which suggests that ICP might be one of the influential factors in the pathophysiology of glaucoma[10]. However, ICP monitoring is not employed in daily practice for glaucoma patients due to its invasiveness. In the case of aerospace medicine, visual impairment of astronauts who are exposed to long-term microgravity is induced by changes in ICP[11], which must be monitored non-invasively in this case. Unfortunately, such a non-invasive device is not available in clinical practice.

Ragauskas et al. reported a novel non-invasive snapshot method for the measurement of ICP based on the two-depth transcranial Doppler (TCD) technique, which can be used for simultaneously measuring blood flow

[1]Health Telematics Science Institute, Kaunas University of Technology, K. Barsausko Str. 59-A556, 51423 Kaunas, Lithuania. [2]Laboratory of Combustion Processes, Lithuanian Energy Institute, Breslaujos Str. 3, 44403 Kaunas, Lithuania. ✉email: yasin.hamarat@ktu.lt

velocities in the intracranial and extracranial segments of the ophthalmic artery (OA)[12]. In this method, the intracranial segment of the ophthalmic artery (IOA) is compressed by ICP while the extracranial segment of the ophthalmic artery (EOA) is compressed by externally applied pressure (Pe). Blood flow velocity parameters in both of these OA segments are approximately equal when Pe = ICP. A review paper has discussed many TCD-based methodological approaches for non-invasive ICP monitoring, and the overall accuracy is around ± 12 mmHg[13]. The innovative two-depth TCD-based non-invasive ICP snapshot measurement technique has clinically acceptable accuracy, precision, and diagnostic reliability[14–16].

The aim of this study was to investigate the possibility of using the OA as a pressure sensor for continuous ICP monitoring. The idea is that periodic non-invasive ICP snapshot measurements[12] could be used for non-invasive recalibration of a non-invasive ICP monitoring method. A key problem in glaucoma diagnosis and treatment is minimizing the deformation of the lamina cribrosa caused by the pressure difference between the intraocular pressure (IOP) and ICP (IOP-ICP)[17]. Our previous studies showed that our non-invasive ICP snapshot measurement method is accurate and precise enough to be applied for abnormally low ICP value diagnosis in normal-tension glaucoma (NTH) and high-tension glaucoma (HTG) patients[10,18].

ICP and IOP have circadian fluctuations over time, so snapshot measurements of these pressures at a certain time do not provide sufficient diagnostic information[19,20]. The monitoring of ICP and IOP is needed for precise and individual patient specific NTG and HTG diagnosis in cases where ICP values are below the normal range. In this study, numerical modeling was employed to investigate the possibility of using OA as an ICP sensor for monitoring. Then, a pilot clinical study was conducted to obtain the first clinical evidence on the linearity and accuracy of the OA as an ICP sensor.

Methods

Numerical modeling of ophthalmic artery as a pressure sensor. To understand and prove the concept of the non-invasive ICP monitoring method, it is important to estimate how the dynamics of the blood flow in the OA is affected during the monitoring procedure. Therefore, numerical modeling was performed on a straight idealized OA (Fig. 1).

COMSOL Multiphysics software (v.5.1 COMSOL AB, Stockholm, Sweden) was used to solve the fluid–structure interaction (FSI) model of a compliant OA while considering the two-way coupling between the pulsatile blood flow and the artery wall (please see Online Appendix 1 for more details).

The following values of acting pressures were considered and used only for numerical modeling of non-invasive ICP snapshot measurements: ICP = {0, 10, 20, 30} mmHg[21], intraorbital pressure Pio = 4 mmHg[22], and Pe = [0:2:34] mmHg[12,23,24].

For every combination of the considered parameters, three cardiac cycles were modeled. During the initial cardiac cycle, all the acting pressures were ramped up from zero to the prescribed values, while during the second cardiac cycle the momentum produced by the initial ramp-up settled down. The difference of the temporal results of the cross-sectional areas at presumable measurement locations of OA between the second and third heart pulse cycle differed by less than 0.01% over the complete cardiac cycle. Therefore, it was concluded that the momentum produced by the initial ramp had negligible influence on the results of the third heart pulse cycle, and the results of the third cardiac cycle were used for the analysis by collecting data at every 0.004 s. This resulted in a 250 time moments per cardiac cycle.

Blood flow factor used for the non-invasive ICP monitoring. The cross-sectional areas in the intracranial and the extracranial segments of the OA depend on the pressures acting on the walls of the OA. Furthermore, the cross-section area of the artery is associated with the intensity of the Doppler signal (Online Appendix 2). Consequently, variations of the OA's cross-sectional area in the intracranial and extracranial segments can be related to ICP by the integral factors derived from the intensity of the Doppler signal. We constructed the blood flow factor BFF for non-invasive ICP monitoring as an integral of the logarithm of the ratio of the Doppler signal intensity P_s obtained from the IOA and the EOA segments of the OA (Online Appendix 2).

Clinical material. The non-invasive ICP ($ICP_{non\text{-}inv}$) monitoring method was investigated clinically after numerical modeling. This pilot study was conducted at the Department of Neurosurgery, Republic Vilnius University Hospital. The study was based on 7 TBI patients that underwent surgery, during which ICP monitoring sensors were implanted. The exclusion criteria were age less than 18 years and a lack of invasive ICP or arterial blood pressure (ABP) data.

The study was approved by the Vilnius Regional Biomedical Research Ethics Committee (No. 158200-15-801-323, date: 2015-10-06), and parents/legal representative of participants provided written informed consent, according to the Declaration of Helsinki. ICP monitoring data were collected between May 2016 and January 2018.

ICP monitoring and data sampling. The simultaneous invasive and non-invasive ICP monitoring is illustrated in Fig. 2. Invasive ICP was measured by a Codman ICP monitor with a catheter tip sensor (Johnson & Johnson Professional, Inc., Raynham, MA, USA). It was sampled at 300 Hz and recorded on a computer by ICM+ software (version 8.2; ICM+ software, University of Cambridge, UK) with a vital sign monitor (Datex-Ohmeda, Inc., Madison, WI, USA).

In the case of non-invasive ICP monitoring, a 2-MHz ultrasonic transducer was mounted on an individually fitted head frame. The locations of the IOA and EOA segments were determined using the edge of the internal carotid artery as a reference point[25]. The blood flow velocities of both segments of the OA were recorded using a two-depth TCD. Signal processing was performed to remove artifacts and to calculate BFF data points with a

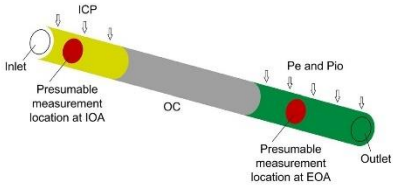

Figure 1. Diagram of the numerical model of an idealized straight ophthalmic artery. *ICP* intracranial pressure, *Pe* externally applied pressure, *Pio* the intraorbital pressure, *IOA* intracranial segment of the ophthalmic artery, *EOA* extracranial segment of the ophthalmic artery, *OC* optic canal.

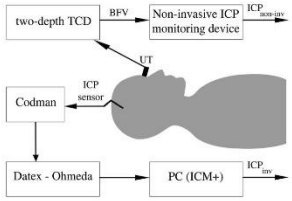

Figure 2. The set-up for simultaneous invasive and non-invasive intracranial pressure monitoring. *UT* ultrasonic transducer, *BFV* blood flow velocity, *TCD* transcranial Doppler, ICP_{inv} invasively monitored intracranial pressure, $ICP_{non\text{-}inv}$ non-invasively monitored intracranial pressure.

sampling frequency of 0.1 Hz. In this pilot study, individual invasive ICP readings were used for initial patient specific BFF data calibration to obtain non-invasive ICP values in pressure units. Next, we monitored ICP continuously for a 1 h period without recalibration. In contrast to the non-invasive ICP snapshot measurement method, Pe was not needed for the non-invasive ICP monitoring procedure.

Statistics. Typically, one paired set of ICP_{inv} and $ICP_{non\text{-}inv}$ data points was obtained every 10 s, resulting in a total of 360 data points during a 1 h monitoring session.

Paired data were analyzed using a Bland–Altman analysis. Linear regression analysis was used to test the hypothesis that the OA can be used as a linear ICP sensor.

MATLAB software (version R2015b; MathWorks Corporation, Natick, MA, USA) was used to process the data and to perform the Bland–Altman and linear regression analyses.

Results

Numerical modeling. The blood flow velocities were extracted at the presumed $ICP_{non\text{-}inv}$ monitoring locations in the IOA and EOA segments (Table 7 in Appendix 1). The obtained blood flow velocities were averaged across the artery lumen cross-sections in their vicinity and over the cardiac cycle. The difference between the resulting velocities in IOA and EOA segments is noted as Δv, which is close to zero when Pe is about 6 mmHg lower than the ICP (Fig. 3). This suggests that the systematic error of the physical $ICP_{non\text{-}inv}$ monitoring is about 6 mmHg.

Part of this error is due to the intraorbital pressure, which was Pio = 4 mmHg in our case. Another part is due to the ophthalmic arterial pressure gradient, which was 1.25 mmHg. Such systematic errors are known a priori, so they can be eliminated in a software solution provided with the proposed non-invasive ICP monitoring technology. Consequently, the patient-specific component produced systematic error less than 1.0 mmHg. The patient-specific component incorporated the arterial pulse wave and the patient-specific mechanical non-equivalence between OA segments, which are not known a priori.

Clinical study. Demographic data and clinical conditions of the patients are presented in Table 1. An individual linear calibration equation (Table 2) was used for each patient to calibrate BFF data points to derive non-invasive ICP values in pressure units. Then, the obtained values were compared with simultaneously monitored ICP_{inv}. One out of the 7 patients was excluded due to invasive ICP or ABP not being monitored. TCD signal artifacts were then removed, after which a total of 1928 paired data points were obtained for the final compari-

Pat. no	Age, years	Gender	GCS on admission	Diagnosis	Surgery type	GOS
1	44	Male	3	DAI with skull open fractures	Intraparenchymal ICP	1
2	39	Male	8	DAI, SDH	Intraparenchymal ICP	5
3	26	Female	7	DAI, SDH	Intraparenchymal ICP	1
4	29	Female	5	DAI	Intraparenchymal ICP	4
5	20	Female	4	DAI	Intraparenchymal ICP	3
6	20	Male	7	DAI	Intraparenchymal ICP	3

Table 1. Demographic data and clinical conditions of the patients included in this pilot study. *GCS* Glasgow coma scale, *GOS* Glasgow outcome scale, *DAI* diffuse axonal injury, *SDH* subdural hematoma, *ICP* intracranial pressure.

Pat. no	Range of ICP_{inv}, min–max, mmHg	Calibration equation used to calculate $ICP_{non\text{-}inv}$	Measured differences, mean ± SD mmHg	Number of paired data points
1	12–22	$56.3 \times \overline{BFF} + 10.1$	0.43 ± 0.91	223
2	16–19	$263.8 \times \overline{BFF} + 11.8$	− 0.22 ± 1.23	360
3	8–11	$70.4 \times \overline{BFF} + 6.2$	− 0.65 ± 1.07	356
4	10–19	$218.9 \times \overline{BFF} + 4.5$	1.61 ± 1.61	280
5	8–10	$109.8 \times \overline{BFF} + 3.8$	0.18 ± 0.64	360
6	13–17	$586.2 \times \overline{BFF} + 6.9$	− 0.39 ± 1.20	349

Table 2. The individual parameters obtained from each patient included in this pilot study.

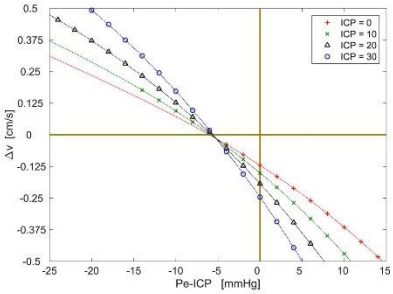

Figure 3. The difference of the blood flow velocities between presumed $ICP_{non\text{-}inv}$ locations in the intracranial and extracranial segments of the ophthalmic artery with respect to the intracranial and extracranial pressures. The polynomial curves are fitted to the data points.

son. The corresponding individual numbers of paired data points are presented in Table 2. The total mean and SD of the measured differences between ICP_{inv} and $ICP_{non\text{-}inv}$ are 0.086 ± 1.34 mmHg. The individual means and SD are presented in Table 2.

As an example, Fig. 4 shows a plot of 223 paired invasive and non-invasive ICP monitoring data points of the first patient. A 60-s moving average filter was used for smoothing both readings. The maximum difference between the paired data points was 1.61 mmHg. The measured differences between ICP_{inv} and $ICP_{non\text{-}inv}$ of all 6 patients are presented in Fig. 5 as a Bland–Altman plot. The extremes of the measured differences between ICP_{inv} and $ICP_{non\text{-}inv}$ are − 3.94 and 4.68 mmHg, and 95% of the observations fall in the interval of − 2.55 to 2.72 mmHg.

The regression analysis showed that there is a strong positive relationship (r = 0.94) between the data obtained with two-depth TCD and the Codman ICP monitor (Fig. 6). The linear equation y = 0.94x + 0.84 demonstrates that OA can be used as a linear pressure sensor with a bias (systematic error) of 0.84 mmHg in the tested ICP range.

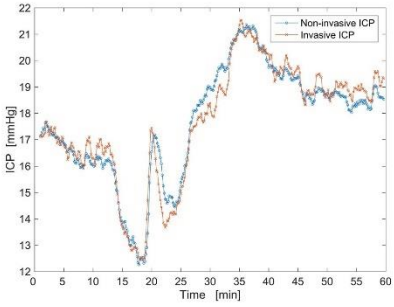

Figure 4. An example of paired invasive and non-invasive ICP data points of the first patient after filtering (60-s moving average filter).

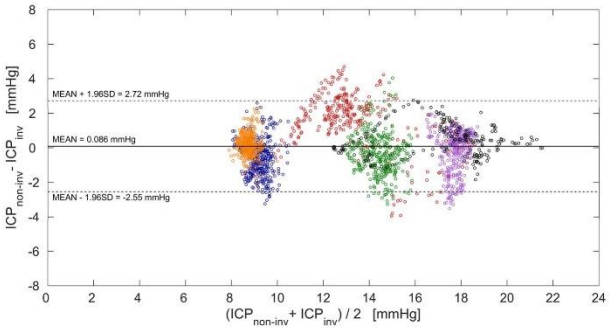

Figure 5. Bland–Altman plot showing the distribution of the measured differences between intracranial pressure monitored directly using invasive Codman ICP monitor (ICP_{inv}) and indirectly using two-depth transcranial Doppler ($ICP_{non\text{-}inv}$) in the entire pressure range obtained in all six patients. Paired data points collected from each of the six patients are separated by colors: first patient—black, second patient—violet, third patient—blue, fourth patient—red, fifth patient—orange, sixth patient—green. The thick horizontal line indicates the total mean of the measured differences, while the two dashed horizontal lines indicate the standard deviation (SD) of ± 1.96 of the measured differences.

Discussion

ICP monitoring has been used for decades in the management of TBI patients[26]. However, the demand for ICP monitoring is also increasing in the fields of ophthalmology[6,8,9,18] and aerospace medicine[11,27]. In this study, we investigated the possibility of using the OA as a pressure sensor for non-invasive ICP monitoring based on two-depth TCD.

The modeling was performed to investigate the blood flow dynamics in the OA and the possible systematic error due to several mechanisms: the ophthalmic arterial pressure gradient, intraorbital pressure, arterial pulse wave, and patient-specific mechanical non-equivalence between IOA and EOA segments. The results of the modeling showed that errors of 4 mmHg and 1.25 mmHg were produced by the intraorbital pressure and the average ophthalmic arterial blood pressure gradient, respectively. The average ophthalmic arterial blood pressure gradient corresponds well with the theoretical value of 1.225 mmHg based on the Hagen–Poiseuille flow assumptions. The patient-specific component, resulting from the arterial pulse wave and the mechanical non-equivalence

produced an error less than 1.0 mmHg. This error is unknown a priori, so it sets possible limiting boundaries for the random error. Based on the clinical standards the random error should be close to ± 2 mmHg[28].

Previous studies showed that the systematic error of the modeled $ICP_{non\text{-}inv}$ monitoring based on the blood velocity was within the limits of [1.6, 1.8] mmHg for the idealized straight OA and [0.04, 4.6] mmHg for the subject-specific curved OA[29,30], which are similar to the value of ± 1.0 mmHg obtained in this study. The current state of the neuroimaging techniques allows for the implementation of subject-specific models considering the OA branching from the internal carotid artery. This allows for the quantitative estimation of the $ICP_{non\text{-}inv}$ monitoring process and more detailed reasoning about the systematic error in specific patients.

In the pilot study, the non-invasive ICP monitoring method showed a strong positive correlation (r = 0.94) with invasively monitored ICP data. In order to test our hypothesis about the linearity of the OA results, invasive ICP values were used for initial calibration, which means the non-invasive two-depth TCD data is converted into non-invasive ICP values in pressure units. The regression analysis showed that the OA can act as a linear ICP sensor in the tested ICP range.

Several important limitations of our study must be mentioned. The main limitation of this pilot study is the small number of patients with relatively narrow ICP variation (8–22 mmHg). A substantially larger sample of patients with different conditions would guarantee the achievement of statistical significance in a prospective study. At the same time, the OA would be tested as a pressure sensor in a wide range of ICP values. Next, the reproducibility of the proposed method was not investigated in this study, although it has been tested by removing and re-applying the head frame in an ICP snapshot measurement study[14]. Both non-invasive ICP monitoring and snapshot measurement methods employ the same principles, which involve locating OA segments and using two-depth TCD data acquisition.

The accuracy of the ventricular ICP monitor depends on periodical recalibration by opening the transducer to atmospheric pressure and returning it to a zero reference point[31]. The patient positioning in relation to the transducer affects the accuracy of ICP readings[32]. The complications in the case of ventricular catheters included a 1–10% risk of infection and a 1–2% risk of bleeding[33]. Parenchymal monitoring devices also require calibration and zeroing, and the pneumatic ICP monitor even runs recalibration every 15 min during monitoring. The risk of complication in the case of parenchymal monitoring is lower compared to ventricular catheters, but it still exists nonetheless[33].

The suggested method can monitor ICP non-invasively for up to one hour without recalibration. We used invasive ICP sensor data for initial calibration in this study, but a non-invasive ICP snapshot measurement method that has clinically acceptable accuracy and precision[14,16] could be used for the initial calibration and periodic recalibration. In this case, the suggested method would be completely non-invasive and avoid any complications caused by invasive procedures.

Conclusion

The numerical modeling and pilot clinical study have demonstrated that the OA can be used as a pressure sensor for non-invasive ICP monitoring. We have observed that it is possible to monitor ICP non-invasively for a one hour without recalibration. This technology could solve the problems of ICP monitoring and diagnosis in conscious subjects, including open-angle glaucoma patients. Nevertheless, further studies are needed to investigate the method in patients with relatively low and high ICP values.

Appendix 1: Numerical modeling of ophthalmic artery as a pressure sensor

The non-invasive intracranial pressure ($ICP_{non\text{-}inv}$) monitoring was investigated numerically while considering an idealized, straight, compliant OA composed of the intracranial (IOA), optic canal (OC), and extracranial (EOA) segments. The lengths of the IOA, OC, and EOA segments used were those most commonly found in humans (Table 3).

The OA lumen volume and wall thickness were assumed to be unaffected by aging or any other processes (Table 3).

The material properties of the blood and OA wall corresponded to those of an average healthy human (Table 4).

The blood was modeled as an incompressible, homogenous, Newtonian fluid[34]. From basic theoretical considerations, the Reynolds number in the OA was calculated as less than 150, while the Womersley number was less than 1, which correspond to the prescribed laminar, fully developed velocity profile at the inlet. The magnitude of the blood flow velocity changed over time according to the typical OA velocity waveform (Fig. 7). To the best of our knowledge, only the peak ophthalmic arterial blood pressure values are available[35]. Therefore, the ophthalmic arterial blood pressure waveform was prescribed at the outlet as a rescaled version of the velocity waveform with the peak pressure values corresponding to those of a healthy human (Table 5).

To capture the exponential stiffening and the anisotropy, the OA walls were modelled as a fiber-reinforced, hyperelastic, nearly incompressible material with two mechanically equivalent fiber families[36]. To the best of our knowledge, the values of the additional artery wall parameters, required by the constitutive material model for the OA wall are unavailable, so internal carotid artery parameters were used instead (Table 6). The mean fiber directions of the two fiber families were defined according to a previously proposed method[29].

The IOA segment was compressed by the ICP. No additional pressure acted on the OC segment, and the EOA segment was compressed by the intraorbital pressure (Pio) and the added external pressure (Pe). It was assumed that ICP, Pio, and Pe were uniformly distributed on the outer surface of the artery wall. To limit the rigid artery wall motion, a spring foundation with a relatively small a spring constant was prescribed on the interface boundary such that would not alter the stress field.

OA wall parameters	Value (mm)
initial lumen diameter	1.3
length of the OA [39]	25.783
length of (IOA) [39]	4.116
length of (OC) [40]	12
length of (EOA) [39]	9.667
wall thickness [41]	0.177

Table 3. Geometrical parameters of the ophthalmic artery. *OA* the ophthalmic artery, *IOA* intracranial segment of the ophthalmic artery, *EOA* extracranial segment of the ophthalmic artery, *OC* optic canal.

	Value	Units
Blood properties		
Effective dynamic viscosity [42]	0.003675	Pa·s
Density [43]	1060	$kg \cdot m^{-3}$
OA wall properties		
Density [44]	1100	$kg \cdot m^{-3}$

Table 4. Basic parameters of blood and wall of the ophthalmic artery.

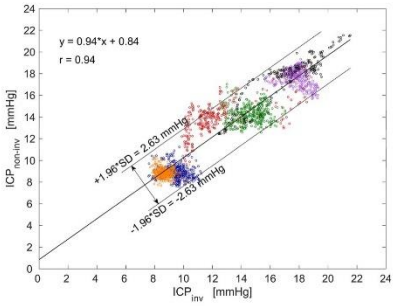

Figure 6. A linear regression graph of all data points shows a strong positive relationship (r = 0.94) between the non-invasively obtained intracranial pressure values ($ICP_{non\text{-}inv}$) and the invasive ICP values (ICP_{inv}). Paired data points collected from each of the six patients are separated by colors: first patient—black, second patient—violet, third patient—blue, fourth patient—red, fifth patient – orange, sixth patient—green.

The geometry was discretized into 71,644 finite elements with 49,734 linear elements for the blood domain and the remaining 21,910 quadratic elements for the artery wall domain.

The fluid–structure interaction (FSI) model considering the two-way coupling between blood and artery wall was solved with COMSOL Multiphysics software (v.5.1. COMSOL AB, Stockholm, Sweden). The Navier–Stokes equations in the Arbitrary Lagrangian Eulerian (ALE) formulation were used to describe the dynamics of the blood flow, while the equation of motion in the material configuration was used to describe the dynamics of the artery walls. The computational mesh of the blood domain was moved according to the Winslow smoothing method[37,38]. A linear MUltifrontal Massively Parallel Sparse direct Solver (MUMPS) was used in conjunction with a nonlinear Newton method. For time stepping, the variable-order-accuracy (from first to second) Backward Differentiation Formula (BDF) solver was used with an adaptive time stepping routine. A relative global tolerance of 10^{-3} and a scaled global absolute tolerance of 5×10^{-4} were used for all solved variables (Table 7).

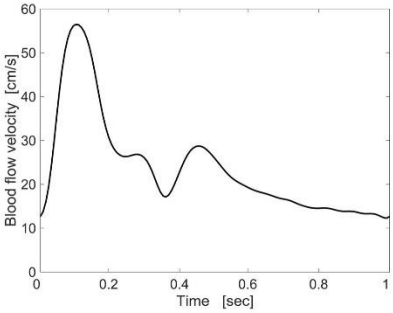

Figure 7. Typical maximum blood flow velocity waveform in ophthalmic artery that was implemented in the numerical model.

Simulation parameters	Value	Units
Duration of one heartbeat pulse cycle [45]	1	s
Systolic arterial blood pressure [35]	80	mmHg
Diastolic arterial blood pressure [35]	40	mmHg

Table 5. Basic simulation parameters.

Arterial wall parameters	Value
Isotropic, kPa	29.7
Anisotropic, kPa	27.8
Anisotropic,	64.2
Fiber angle, deg	22.0
Dispersion,	0.8

Table 6. Ophthalmic artery wall parameters used for fiber-reinforced double layer model based on internal carotid artery wall parameters according to [46].

Simulation parameters	Value (mm)
distance from the OA starting location at which the data was collected at IOA segment	2.058
distance from the OA starting location at which the data was collected at EOA segment	20.834

Table 7. Locations of cross-sections were data was extracted. *OA* the ophthalmic artery, *IOA* intracranial segment of the ophthalmic artery, *EOA* extracranial segment of the ophthalmic artery.

Appendix 2: Definition of blood flow factor used for non-invasive ICP monitoring

The variations of the blood flow velocity parameters and OA cross-sectional area in the IOA and EOA can be compared by the integral factors derived from the intensity of the reflected ultrasound Doppler signal. The blood flow factor (*BFF*) is defined as an integral of the difference of logarithms of Doppler signal intensity P_s obtained from the IOA and EOA:

$$BFF(t) == \int_{\tau=0}^{10} \int_{u} \left| ln\left(\frac{P_{su,IOA}(t-\tau,u)}{P_{su,EOA}(t-\tau,u)} \right) \right| du\, d\tau\,,\ t = [10,\ 20, \ldots,\ 3590]\, s, \quad (1)$$

where $P_{su}(t, u)$—is the ultrasound signal intensity distribution over the velocity u measured by the Doppler signal. In order to compare *BFF* with the ICP monitored non-invasively, the factors were processed. The factor *BFF* and

invasively monitored ICP_{inv} were smoothed by a moving average with $T_{smooth} = 60$ s, and the smoothed factor $\overline{BFF}$ was rescaled according to $\overline{ICP_{inv}}$ values by:

$$f(t) = a + b \cdot \overline{BFF}(t). \quad (2)$$

The scale coefficients a and b must satisfy the condition of equality of standard deviations and the means of rescaled factor f and $\overline{ICP_{inv}}$:

$$\begin{cases} std(f(t)) = std(\overline{ICP_{inv}}(t)) \\ mean(f(t)) = mean(\overline{ICP_{inv}}(t)) \end{cases}, t = [T_{smooth}, t_{end}], \quad (3)$$

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Author contributions
Conceptualization: A.D. and L.B. Data curation: L.B., R.Z., E.M., A.D. and Y.H. Formal analysis: P.L., E.M., A.D. and Y.H. Funding acquisition: R.Z. Methodology: R.Z. and A.D. Software: M.D., L.B. and E.M. Visualization: L.B., E.M. and Y.H. Writing—original draft: P.L., L.B., E.M. and Y.H. Writing—review & editing: L.B., E.M., A.D. and Y.H.

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Additional information
Correspondence and requests for materials should be addressed to Y.H.

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Review

Can the Treatment of Normal-Pressure Hydrocephalus Induce Normal-Tension Glaucoma? A Narrative Review of a Current Knowledge

Yasin Hamarat [1,*], Laimonas Bartusis [1], Mantas Deimantavicius [1], Paulius Lucinskas [1], Lina Siaudvytyte [2], Rolandas Zakelis [1], Alon Harris [3], Sunu Mathew [3], Brent Siesky [3], Ingrida Janulevicienė [2] and Arminas Ragauskas [1]

[1] Health Telematics Science Institute, Kaunas University of Technology, K. Barsausko Str. 59-A557, LT-51423 Kaunas, Lithuania; laimonas.bartusis@ktu.lt (L.B.); Mantas.Deimantavicius@ktu.lt (M.D.); Paulius.Lucinskas@ktu.lt (P.L.); rolandas.zakelis@ktu.lt (R.Z.); telematics@ktu.lt (A.R.)
[2] Eye Clinic, Lithuanian University of Health Sciences, Eiveniu Str. 2, LT-50009 Kaunas, Lithuania; lynciuke@gmail.com (L.S.); ingrida.januleviciene@kaunoklinikos.lt (I.J.)
[3] Glaucoma Research and Diagnostic Center, Eugene and Marilyn Glick Eye Institute, Indiana University School of Medicine, Indianapolis, IN 46202, USA; alharris@indiana.edu (A.H.); sunumath@iupui.edu (S.M.); bsiesky@indiana.edu (B.S.)
* Correspondence: yasin.hamarat@ktu.lt

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Abstract: Ventriculoperitoneal shunt placement is the most commonly used treatment of normal-pressure hydrocephalus (NPH). It has been hypothesized that normal-tension glaucoma (NTG) is caused by the treatment of NPH by using the shunt to reduce intracranial pressure (ICP). The aim of this study is to review the literature published regarding this hypothesis and to emphasize the need for neuro-ophthalmic follow-up for the concerned patients. The source literature was selected from the results of an online PubMed search, using the keywords "hydrocephalus glaucoma" and "normal-tension glaucoma shunt". One prospective study on adults, one prospective study on children, two retrospective studies on adults and children, two case reports, three review papers including medical hypotheses, and one prospective study on monkeys were identified. Hypothesis about the association between the treatment of NPH using the shunt to reduce ICP and the development of NTG were supported in all reviewed papers. This suggests that a safe lower limit of ICP for neurological patients, especially shunt-treated NPH patients, should be kept. Thus, we proposed to modify the paradigm of safe upper ICP threshold recommended in neurosurgery and neurology into the paradigm of safe ICP corridor applicable in neurology and ophthalmology, especially for shunt-treated hydrocephalic and glaucoma patients.

Keywords: normal-pressure hydrocephalus; normal-tension glaucoma; ventriculoperitoneal shunt; intracranial pressure; lamina cribrosa

1. Introduction

Normal-pressure hydrocephalus (NPH) is a neurological disease characterized by enlarged cerebral ventricles and clinical features of gait disturbance, urinary incontinence, and cognitive decline [1–3]. Dilation of ventricles is caused by a disturbance in the cerebrospinal fluid (CSF) pathway from production to absorption locations [4]. As the name of this disease suggests, intracranial pressure (ICP) remains in the normal range most of the time [5]. However, the name of normal-pressure hydrocephalus is misleading because continuous monitoring of ICP shows intermittently raised ICP in association with pressure waves [6]. NPH is generally considered to be a disorder of adult and geriatric patients. Around 5.5 patients per 100,000 population undergo ventriculoperitoneal (VP) shunt placement for the treatment of NPH annually, representing one of the commonly performed

neurosurgical interventions [7]. VP shunt placement relieves this life-threatening disorder [8], but a hypothesis has recently emerged that treatment of NPH is associated with the development of normal-tension glaucoma (NTG) [9,10].

Glaucoma is a chronic, multifactorial optic nerve (ON) disease characterized by progressive retinal nerve fibers and visual field decline [11]. NTG is a subset of open-angle glaucoma in which intraocular pressure (IOP) is normal (IOP $\leq$ 21 mmHg), in contrast to high-tension glaucoma (HTG) in which IOP is above 21 mmHg [11,12].

The purpose of this article is to review the literature published regarding the association between the treatment of NPH and the development of NTG, to emphasize the need for neuro-ophthalmic follow-up for patients with shunt-treated NPH.

1.1. Pathophysiologic Mechanism of ON Damage in NTG

The pathology of glaucoma may worsen progressively and irreversibly even in cases where IOP, the main risk factor for glaucoma, does not exceed the normal range. Thus, the cause of ON damage in NTG remains a mystery.

It has been suggested that disturbances in ocular blood flow are a major risk factor in the pathogenesis of NTG [13,14]. Vascular complication, such as vasospasms, vasosclerosis, small vessel disease, and autoregulatory dysfunction, leading to perfusion deficits of the ON head, the retina, the choroid or the retrobulbar vessels, might influence the loss of retinal nerve fibers [13,15]. Systemic hypotension, particularly nocturnal arterial hypotension, is another risk factor that is believed to influence the progression of glaucoma [16,17]. Ocular perfusion pressure is defined as the difference between arterial blood pressure (ABP) and IOP. Thus, low ABP causes low ocular perfusion pressure, and this results in ischemic damage to the ON [16]. Yet other pathogenetic factors, such as autoimmunity [18,19], inflammation [20], and accumulation of toxins [21], are believed to contribute to the development of NTG.

Currently, attention has been focused on the idea formulated by Volkov back in 1976 that a low ICP may be involved in the pathogenesis of glaucomatous optic neuropathy, because the ON immediately beyond the lamina cribrosa (LC) is surrounded by CSF [22]. Schematic representation of the relevant intraocular/retrolaminar space is depicted in Figure 1 for the explanation of this hypothesis.

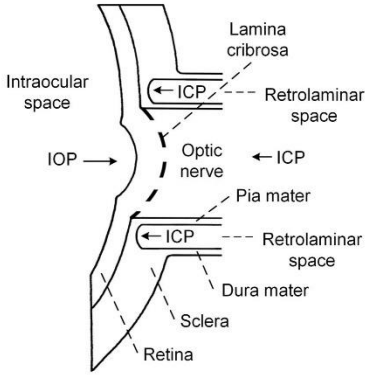

Figure 1. Schematic representation of the relevant intraocular/retrolaminar space. IOP—intraocular pressure, ICP—intracranial pressure.

The LC is a sieve-like structure, through which the retinal ganglion cell axons pass before forming the ON [23]. The retrolaminar space is a CSF-filled compartment surrounding the ON immediately posterior to the LC [24]. The LC separates the intraocular and retrolaminar spaces and is the possible location of axonal injury.

The pressure change across the LC, called translaminar cribrosa pressure gradient (TCPG), has been proposed to be the primary factor responsible for axonal injury [24,25]. TCPG is calculated as TCPG = (IOP-ICP)/thickness of the LC. According to this hypothesis, TCPG increases due to increased IOP or decreased ICP, and could be responsible for ON damage [26]. In the case of NTG, IOP is within a normal range; therefore, decreases in of ICP might be the cause of ON damage.

The first evidence in favor of this hypothesis appeared in 1979, 3 years after the publication by Volkov. In an experimental study, Yablonski et al. slightly decreased the ICP below the atmospheric pressure by cannulating the cisterna magma in cats [27]. The IOP in one eye was decreased to slightly exceed atmospheric pressure by cannulation of the anterior chamber, whereas the remaining eye was left untouched. After 3 weeks, the optic disc of the eye in which IOP was unchanged showed glaucomatous optic neuropathy; in contrast, no sign of glaucoma was identified in the eye that had reduced IOP. Since then, little attention has been focused on the role of ICP in the development of glaucoma until recent years.

In a retrospective study, Berdahl et al. reviewed the medical records of 62,468 patients who had lumbar puncture readings [28]. These authors selected 57 open-angle glaucoma patients (including 11 NTG patients) and 105 age-matched control subjects (patients with no signs of glaucoma) for the comparison of ICP. The mean ICP was significantly lower in open-angle glaucoma patients (9.6 $\pm$ 3.1 mmHg) and NTG patients (9.3 $\pm$ 3.2 mmHg) compared with control subjects (12.7 $\pm$ 3.9 mmHg).

In a prospective study, Ren et al. measured ICP via lumbar puncture on 29 HTG patients, 14 NTG patients and 71 subjects without glaucoma [29]. The mean ICP was significantly lower in NTG patients (9.5 $\pm$ 2.2 mmHg) than in the control subjects (12.9 $\pm$ 1.9 mmHg) and HTG group (11.7 $\pm$ 2.7 mmHg).

In a prospective pilot study, Siaudvytyte and colleagues measured ICP using a novel two-depth transcranial Doppler (TCD) based non-invasive ICP measurement device, including nine patients with NTG, nine patients with HTG, and nine healthy controls [30]. The mean ICP was found to be lower in NTG patients (7.4 $\pm$ 2.7 mmHg) than healthy controls (10.5 $\pm$ 3.0 mmHg) and the HTG group (8.9 $\pm$ 1.9 mmHg), although differences between the groups were not statistically significant.

In a most recent prospective study, conducted by Linden and colleagues, ICP was measured via lumbar puncture by using the Likvor CELDA system on 13 NTG patients and 51 healthy volunteers [31]. The mean ICP measured in a supine body position was lower in the NTG patients (10.3 $\pm$ 2.7 mmHg) than healthy volunteers (11.3 $\pm$ 2.2 mmHg). However, differences between the groups were not statistically significant.

Although all four studies showed lower mean ICP values measured on NTG patients compared with control subjects, a final conclusion in favor of the proposed hypothesis cannot yet be stated. The largest study was retrospective, and the remaining three, although prospective, did not enroll a large group of NTG patients and could be titled pilot studies.

Dysfunction of an occlusion mechanism of the ON sheath around the ON has been proposed recently as a pathophysiologic component in NTG [32]. The unifying glymphatic hypothesis of glaucoma, which incorporates vascular, biomechanical, and biochemical factors to explain the pathophysiology of glaucomatous optic neuropathy, has also been proposed [25,33].

1.2. Association between NPH and NTG

The possible role of decreased ICP in the development of NTG is relevant to the treatment of NPH. Guidelines for the management of NPH indicate that the most effective treatment is surgical procedures during which either ventriculoperitoneal, ventriculoa-

trial, or lumboperitoneal shunts are implanted [34]. According to structural features, the shunt systems are categorized into four groups: fixed differential pressure valves, programmable valves, gravity-assisted valves, and flow-regulated valves. Currently, there is no generally established method for setting the initial valve pressure value. Low pressure (0.4–3.7 mmHg) or medium pressure (3.8–8.1 mmHg) fixed differential pressure valves have been recommended and used [34]. Reference tables to set the initial pressure value of the programmable valves based on the patient's height and weight have been suggested [34,35]. These pressure values range from 2.2 mmHg to 14.7 mmHg for males and females. Mean ICP values measured on NTG patients (9.3 ± 3.2 mmHg [28], 9.5 ± 2.2 mmHg [29], 7.4 ± 2.7 mmHg [30], 10.3 ± 2.7 mmHg [31]) are even higher compared to recommended initial pressure values of valves used to treat NPH patients.

A question can be raised as follows: does the treatment of NPH by using the shunt to reduce ICP cause NTG? To find the answer, we have performed an online literature search in the database PubMed using the following search terms: "hydrocephalus glaucoma", "normal-tension glaucoma shunt". The references and citation indices of the selected articles were hand-searched for additional relevant articles. Papers have been included in this review after first screening the titles and later reading relevant abstracts with whole articles. One prospective study on adults, one prospective study on children, two retrospective studies on adults and children, two case reports, three review papers, and one prospective study on monkeys were found to be relevant to the question of this paper. A structured comparative description of the studies is depicted in Table 1.

Table 1. Summary of those studies analyzing the association between the treatment of normal-pressure hydrocephalus using a shunt to reduce intracranial pressure and development of normal-tension glaucoma. Review papers are not included in this table.

Study	Method	Sample Size	Age, Years	Study Group	Control Group	Time Frame	Glaucomatous Damage
Gallina P, et al. [26]	Prospective study	12 males, 10 females	Range of 68–87 years	22 adult	-	6 months	9 patients
Yang D, et al. [36]	Prospective study	9 male Rhesus monkeys	An average age of 6 years	4 Rhesus monkeys	5 Rhesus monkeys	12 months	3 Rhesus monkeys
Rudolph D, et al. [37]	Prospective study	32 boys, 24 girls	An average age of 15 years	56 children	-	12 months	13 patients
Chang TC and Singh K. [38].	Retrospective study	67 males, 77 females	An average age of 75 years	72 adult	72 adult	132 months	13 patients
Heinsbergen I, et al. [39]	Retrospective study	67 males, 52 females	Range of 1–5 years	119 children	-	96 months	N/S
Chen BH, et al. [40]	Case report	1 female	93	1 adult	-	162 months	1 patient
Yusuf IH, et al. [41]	Case report	1 male	27	1 adult	-	300 months	1 patient

N/S: not specified.

1.3. Prospective Studies

The prevalence of NTG in patients with NPH who had implanted VP shunt for the treatment was estimated by Gallina et al. [26]. The extent of the ON exposure (time between the shunt placement and ophthalmic examination) to the change of the pressure difference IOP-ICP in relation to NTG occurrence was also evaluated in this study. Nine of 22 patients had NTG, which is 40-fold more compared with the general elderly population without NPH. The authors concluded that the main risk factor for the development of NTG in shunt-treated NPH patients is the duration of ON exposure to the lowering of ICP. According to the authors of this study, the next step should be the determination of tolerated times for a given ICP decrease.

Retinal nerve fiber layer (RNFL) thickness and neuroretinal rim area (NRA) of the ON head were examined after reduction of ICP on Rhesus monkeys [36]. Lumbar-peritoneal CSF shunt was implanted in nine monkeys. The shunt was opened to achieve roughly

3 mmHg of ICP in four monkeys, while the shunt was left closed in five monkeys. A follow-up of 1 year was done by taking optic coherence tomography and photographic images of the ON head and RNFL of all monkeys. At the beginning of the study, RNFL thickness and NRA did not differ significantly between groups of monkeys with an opened shunt and closed shunt. During a follow-up, two monkeys with an opened shunt (50%) demonstrated a progressive reduction in RNFL thickness in both of their eyes, followed by a significant reduction in the NRA. An optic disc hemorrhage was identified at the fourth month after the beginning of the study in the right eye of the third monkey with an opened shunt. Mean RNFL thickness was significantly less in the monkeys with opened shunt 89.4 ± 15 µm than in the monkeys with closed shunt 100.9 ± 7.4 µm at the end of the study. The authors of this study concluded that their findings support the concept that a low ICP might be a risk factor in all forms of optic neuropathy, including glaucoma.

Visual field examination has been performed in children with shunt-treated hydrocephalus by Rudolph et al. [37]. A total of 56 ophthalmological examinations were performed on 32 boys and 24 girls. Visual field testing was possible in 44 cases. The examination was incomplete in 12 patients with cognitive deficits or inadequate compliance. Visual field deficits were observed in 24 patients which is 54.5% of all completed examinations. There were visual field constrictions between 10 degrees and 50 degrees out of the center. The authors concluded that children with shunt-treated hydrocephalus have an increased risk of ophthalmological abnormalities and should be more intensively ophthalmologically monitored.

1.4. Retrospective Studies

Electronic medical records of 72 NPH patients and 72 controls were retrospectively analyzed by Chang and Singh to test the hypothesis that the prevalence of glaucoma is higher in patients with NPH compared to adult age-matched and race-matched controls [38]. These authors estimated that the prevalence of glaucoma in NPH was 18.1% (13 cases) in contrast to 5.6% (four cases) in controls. Authors of this retrospective study concluded that the three-fold greater likelihood of glaucoma diagnosis in the NPH group is a significant finding that deserves further prospective study. However, the number of NTG cases was unknown. Thus, the prevalence of NTG in NPH patients was not determined. Also, the distinction between shunt-treated and non-shunt treated patients was not performed, which made it impossible to separate cases of glaucoma associated with CSF diversion.

Medical records of 137 shunted hydrocephalic children patients were retrospectively reviewed by Heinsbergen et al. to identify the main risk factors for outcome [39]. The type and prevalence of impairment, including visual function, was also listed. One-hundred-nineteen patients were included in the analysis. The diagnosis of hydrocephalus was made in 90% of the patients before the age of 1 year and in rest after 1 year of age. The median age at the assessment of the outcome was 5 years. It was found that 25% of all patients were diagnosed with visual function impairment.

1.5. Case Reports

NTG was diagnosed in a 93-year-old white woman in May 2000 [40]. A VP shunt with a programmable valve set at 8.8 mmHg had been placed in this patient for the treatment of NPH in September 2011. Two optic disc hemorrhages were detected in the right eye and worsening of visual fields in both eyes was noted 1 month after implantation of the VP shunt. The pressure value of the programmable valve was increased up to 14.7 mmHg. After this, ophthalmic examination showed that disc hemorrhages in the right eye had disappeared. Pressure setting of the VP shunt was decreased multiple times because the patient developed signs of NPH; first, from 14.7 to 13.2 mmHg in November 2011; second, from 13.2 to 11.8 mmHg in December 2011; third, from 11.8 to 11.0 mmHg in January 2012; and fourth, from 11.0 to 10.3 mmHg in February 2012. A new optic disc hemorrhage was detected in the right eye, and again worsening of visual fields in both eyes was noted in August 2012. Optic disc hemorrhage was identified in the left eye in September 2013. At this time, the pressure setting of the VP shunt was increased to 11.0 mmHg. No disc

hemorrhages were visible in November 2013. The authors concluded that this case is the first report of worsening of NTG obviously caused by lowering the ICP after implantation of the VP shunt for the treatment of NPH.

A 2-year-old boy developed hydrocephalus after the treatment of malignant pineoblastoma [41]. VP, ventriculopleural, and ventriculoatrial shunts were placed in succession for the treatment of hydrocephalus. The patient underwent eight shunt revisions in a period of 25 years, during which ICP values below the normal range according to the age of the patient have been identified at last six revisions. A diagnosis of juvenile-onset NTG was made in his only seeing left eye after detailed ophthalmic examinations. A programmable shunt has been implanted in the patient at the age of 27 years to relieve headaches and reduce the risk of progressive glaucomatous visual loss. Four weeks after the implantation, the ICP had stabilized at 6 to 13 mmHg, which approximately falls into the normal ICP range at that age (8 to 15 mmHg). The authors concluded that this case describes a human model of juvenile-onset NTG caused by low ICP, in which all other non-IOP-dependent pathophysiological mechanisms have been excluded.

1.6. Review Papers Including Medical Hypotheses

Bokhari and Baeesa described the clinical and theoretical basis for their hypothesis after reviewing literature regarding the increased prevalence of glaucoma among NPH patients treated using a CSF diversion procedure [9]. The authors hypothesized that besides the recently included pathophysiologic mechanism of TCPG increase in the pathogenesis of NTG, inherently fragile neurons in NPH patients could be another possible reason for an increased prevalence of glaucoma. The authors even suggested including TCPG into the treatment guidelines of NPH. They expect that recent advances in the imaging of the ON head complex might provide an opportunity to detect the mechanical changes of an increased TCPG before ON damage happened.

Wostyna et al. have reviewed the literature and discussed low ICP as a risk factor for the development of NTG [42]. As the authors of this paper revealed growing evidence of the important role of low ICP in the pathogenesis of glaucoma, including the development of NTG after treatment of NPH, they hypothesized that in the future, glaucoma could be treated from the intracranial compartment side of the LC. The authors proposed an implantable CSF pump—an invasive system to infuse artificial CSF into the intrathecal space surrounding the spinal cord, thus increasing the ICP—as a novel strategy for the treatment of glaucoma.

McCulley et al. summarized the published works regarding relationships between ICP and glaucoma and the current evidence supporting or denying ICP as a risk factor for glaucoma [24]. Association between NTG and treatment of NPH by the CSF shunting procedure that reduces ICP was also discussed. The authors concluded that already published data support the notion that low ICP is a risk factor for glaucoma and might be responsible for the increased rate of NTG observed in NPH patients.

2. Results

The hypothesis about the association between the treatment of NPH using a shunt to reduce ICP and development of NTG is supported in all above-reviewed retrospective studies, case reports, and review papers. However, these works do not belong to the first-level of evidence in evidence-based medicine. Three prospective studies—with first-level evidence, although all including relatively small sample size (22 adult humans [26], 44 children [37], 9 Rhesus monkeys [36])—also revealed a convincing link between the reduction of ICP and development of NTG. Summarizing all of these results, it seems that a safe lower limit of ICP for neurological patients, especially shunt-treated NPH patients, should be retained. If so, the paradigm of a safe upper ICP threshold (as recommended in neurosurgery ICP < 20 mmHg [43,44] or ICP < 22 mmHg [44,45], and neurology ICP < 14.7 mmHg [46,47]) should be modified into the paradigm of safe ICP corridor ap-

plicable in neurology and ophthalmology, especially for shunt-treated hydrocephalic and glaucoma patients, to avoid progression of NTG.

Although the ICP upper threshold values used to initiate treatment in neurosurgery were recommended many years ago, these are still debatable [44]. Whereas no data are available to formulate recommendations of lower ICP thresholds used to minimize or eliminate the risk of NTG development. There is no well-established technique to set initial postoperative valve pressure value. Reference tables to set the initial pressure value of programmable valves based on the patient's height and weight have been suggested without considering the risk of NTG development [34,35]. These pressure values range from 2.2 mmHg to 14.7 mmHg, both for males and females. Postoperative measurement of ICP using an invasive external ventricular drain or an intraparenchymal monitor is undesirable for shunt-treated patients because of a too high risk of infection, restricted mobility, and short-term use, among other reasons [48]. Most of the time, anamnesis, clinical examination, imaging studies, and the physician's judgment are used to adjust valve settings for proper CSF drainage. However, measurement of ICP would be valuable in postoperative shunt complications, shunt occlusion, infection, headache, and subdural hematoma, among other scenarios.

Gallina et al. suggested not searching for a threshold of ICP itself, but a threshold of IOP–ICP difference (ΔP) multiplied by exposure time (t) of such a difference, because they found that duration of ON exposure to the lowering of ICP is very influential for the development of NTG in shunt-treated NPH patients [26]. First-level evidence studies will be needed to derive these threshold values.

While IOP measurement, although indirect, is non-invasive and easily obtained by using an applanation tonometer, ICP measurement is complicated because invasive procedures, which can be done by a neurosurgeon, are needed to obtain a reliable ICP value. ICP measurement by non-invasive means would enable better postoperative management of shunt-treated patients and would encourage future studies for the search of safe lower ICP or upper $\Delta P \times t$ threshold values. Plenty of the suggested non-invasive ICP assessment approaches, such as measurement of the pulsatility index in the middle cerebral artery, fundoscopy, measurement of the optic nerve sheath diameter, magnetic resonance imaging and assessment of tympanic membrane displacement, are unable to measure absolute ICP value accurately and have not been used in clinical studies for the NTG diagnosis [49,50]. We identified only one (recently published) study on glaucoma patients in which ICP has been measured in a non-invasive manner [30]. A promising two-depth TCD device has been used for the non-invasive measurement of ICP in this prospective pilot study. The accuracy, precision, diagnostic sensitivity, and specificity of this non-invasive ICP technology have been independently tested on neurological patients by various groups [51–53]. Although, the results showed fair agreement to invasively measured ICP with normal, high, or slightly elevated ICP in neurological patients, there is no accurate validation of this technology in a lower range of ICP (0–8 mmHg) tested in NTG patients.

Future advances in two-depth TCD non-invasive ICP measurement technology or other should allow searching for safe lower ICP thresholds which would enable NPH treatment without or with minimal risk of NTG development and would put the paradigm of a safe ICP corridor into clinical practice.

While ICP has recently been considered to influence the development of glaucoma, yet another physiological mechanism also from the intracranial compartment, cerebrovascular autoregulation (CA), started to emerge as a factor that might play a role in the pathogenesis of glaucomatous optic neuropathy [54,55].

3. Conclusions

The available data suggest that there is a link between the treatment of NPH using a shunt to reduce ICP and the development of NTG. Unfortunately, there are no published data on a safe lower ICP patient-specific threshold, which would help to improve NPH

patients while the risk of NTG development would be minimal. Definitively validated non-invasive measurement of ICP would encourage searching for such threshold values.

A limited amount of data also suggests that CA might play a role in the pathogenesis of glaucomatous optic neuropathy. Prospective CA monitoring studies on NPH patients who have a risk of NTG development are now needed.

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Europos socialiniui fondui, Lietuvos mokslo tarybai, Europos regioninės plėtros fondui, Centrinei projektų valdymo agentūrai, Lietuvos sveikatos mokslų universiteto Mokslinių tyrimų ir eksperimentinės plėtros fondui, Kauno technologijos universiteto Inovacijų fondui už paramą projektams.

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