Evaluation of non-invasive intracranial pressure technology for use in glaucoma

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The aims of this study are (1) to determine if ear absorbance can be used to non-invasively measure ICP and (2) to determine if ICP differs between glaucoma patients and controls.

Ethical review	Approved WMO
Status	Will not start
Health condition type	Glaucoma and ocular hypertension
Study type	Observational non invasive

Summary

ID

NL-OMON46482

Source
ToetsingOnline

Brief title
Non invasive ICP measurement technology in glaucoma

Condition

- Glaucoma and ocular hypertension

Synonym
Glaucoma, POAG

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Ministerie van OC&W,European committee and Uitzicht

Intervention

Keyword: Glaucoma, Intracranial Pressure (ICP), Otoacoustic Emission (OAE), Tympanometry

Outcome measures

Primary outcome

Ear absorbance as a function of posture : Postures which provoked high ICP increase perilymphatic pressure which displaces the stapes outward from the oval window, when this happen we can see a smaller absorbance. We should be able to repositioned the stapes using positive air pressure through the ear canal making the absorbance curve equal to the upright position curve and having the same ICP (normal iCP) that in this position.

In the case of low ICP, perilymphatic pressure decrease and displaces the stapes inward of the oval window which should produce a bigger absorbance. We hypothesize that should be used negative pressure by the ear canal for repositioned the stapes in this case.

Necessary pressure (measured in daPa) to repositioned the stapes (putting at the same place that upright position, that mean in a normal ICP) is going to be register in every subject an compared with each group making a t-student test.

Secondary outcome

Phase of DPOAEs as a function of posture.

Study description

Background summary

Glaucoma is a collection of diseases that causes progressive degeneration of optic neurons. Characteristic damage to axonal components of the optic nerve

head and the surrounding neuroretinal rim. Despite advances in clinical management strategies, glaucoma continues to be the leading cause of irreversible blindness worldwide. Glaucoma usually manifests with an elevated IOP which is a causal factor for optic neuronal damage.

Recently, a number of studies have shown that ICP is a significant risk factor for glaucoma. After emerging out of the lamina cribrosa and throughout its whole course, the optic nerve is surrounded and bathed by CSF, running through the subarachnoid space and generating the so-called retrobulbar pressure which in essence is the same as ICP. The lamina cribrosa is under the influence of two separate but possibly interdependent pressures - the posteriorly acting IOP and the anteriorly acting ICP. Recent studies show that ICP is as responsible for causing neuronal damage at the optic nerve head as elevated IOP.

Clinically, when there is an alteration of the ICP may be accompanied by somes symptoms, such as headache, blurred vision, feeling less alert than usual, vomiting, changes in the behavior, weakness or problems with moving or talking and lack of energy or sleepiness. These symptoms can be caused by a bleeding into the brain, too much cerebrospinal fluid, swelling in the brain, aneurysm, blood pooling in some part of the brain, brain or head injury, brain tumor, infections such as encephalitis or meningitis, hydrocephalus, high blood pressure or a stroke.

But there is no validated method to determine the absolute value of ICP. Invasive methods like external ventricular drainage or lumbar punctures present risks such as hemorrhages, subdural hematomas, skin infections, cranial fractures, ventriculitis, meningitis or fatal septicaemia, also technical difficulties as surgical placement of catheters can be present, that limit them to specialized centers. These methods can be repeated only in exceptional cases. However, the ICP is recognized as an important indicator in the follow-up of many pathologies (not only glaucoma).

Non-invasive monitoring of ICP via the auditory system is theoretically possible because changes in ICP transfer to the inner ear through connections between the cerebral spinal fluid and the cochlear fluids. Distortion-product otoacoustic emissions (DPOAE) are produced by couples of pure tones at frequencies fl and f2 that are chosen by the investigator and can take any value between 0.7 and 8 kHz. When there is a damage in the brain (broke, hemorrhage, ischemia, etc) usually that can affect the blood circulation and the CSF which have a decompensation. Recently, we performed a study and showed that distortion product otoacoustic emissions (DPOAEs) are highly sensitive to small changes in ICP induced by changes in body position and these changes were identical in glaucoma patients and controls. However, the concerning method appeared not to allow for an absolute ICP measurement. (Reference study: NL59638.042.16 *A method for non-invasive intracranial pressure measurement in glaucoma*).

The aim of this project is to use an ear property that depends only on the ICP (in any case, the absolute pressure that prevails in the inner ear) and therefore does not require calibration to give access to the absolute ICP. This property is the absorbance (the ability to let in the sound the acoustic energy absorbed by the ear), which is optimal when the vibrating structures are not energized, so when the pressure outside the ear (easy to measure and make in variations in the external auditory canal - CAE) is exactly balanced by the pressure inside. The absorbance measurement is performed routinely during audiological tests, using automated commercialized devices, usable by trained paramedic operator. It presents no risk or discomfort and can be repeated at will.

Measuring absorbance we can understand the changes in the ICP. Changes in the perilymphatic pressure produce variations in the middle ear which influence the contraction of the stapedius muscle attached by a ligament to the stapes which is the responsible of the stapes movement into the oval window. High ICP increase perilymphatic pressure which displaces the stapes outward from the oval window, when this happen we can see a smaller absorbance. In the case of low ICP, perilymphatic pressure decrease and displaces the stapes inward of the oval window which should produce a bigger absorbance.

That mean than perilymphatic pressure can reflect CSF pressure when the cochlear aqueduct is working correctly. Cochlear aqueduct runs from subarachnoid space and allowed the relation between CSF and ear fluids which in the case of be altered would affect also at the middle ear. Thus, if the CSF pressure (and consequently ICP pressure) provoked an alteration in perilymphatic pressure and moving the stapes in the middle ear, we should be able to repositioned the stapes using pressure through the ear canal which will move the stapes and will make a pressure compensation.

The difference between this technique (absorbance) and the DPOAEs technique (reference study: NL59638.042.16) is that with the absorbance we search information about high or low ICP, while DPOAEs give us information about the alteration of the ICP, which is really useful in the clinical practice but less specific.

Recently, a pilot use of a commercial system of absorbance in the development of audiological standards has shown that in 38 ears of healthy subjects between 20 and 30 years, the absorbance is maximum at on average P_cae = 0 mmH2O in standing posture, 13 mmH2O in supine position, and 23 mm H2O in Trendelenburg position (-20 °). This indicates that absorbance is indeed related to ICP. An ear computational model was established from a well-accepted published ear model (Zwislocki, 1963) and this model replicated the observed experimental behavior by attributing the cause of changes in absorbance to ICP.

With this new technique we could avoid the complications in relation to the invasive methods of ICP measuring (hemorrhages, subdural hematomas, skin

infections, etc) and being more specific about hyper/hypo ICP.

Loiselle (2018) (NL59638.042.16) study show how invasive data of ICP and DPOAE phase are linearly related over an ICP of 3mmHg. With this evidence we can continues to investigate about the relation between more ear functions, such as absorbance in the ICP, looking for a more specific information.

In this study we combine absorbance measurements with DPOAEs, where the former should provide an absolute estimate of ICP at different body positions and the latter the change in ICP when going from one position to the other.

Study objective

The aims of this study are (1) to determine if ear absorbance can be used to non-invasively measure ICP and (2) to determine if ICP differs between glaucoma patients and controls.

Study design

Study design:

This study is a cross-sectional, observational study.

Duration: 4 months for recruitment and data collection.

Subjects with healthy eyes who responded to our advertisement (see form E3), and glaucoma patients who were selected from the Groningen Longitudinal Glaucoma Study database, receive the information letter and the informed consent form (see forms E1a-b and E2a-b). After informed consent is obtained, subjects will undergo the following investigations:

Screening:

Healthy subjects will undergo a routine eye screening (see descriptions below), while information from the patients will be taken from their hospital files.

Subjects with healthy eyes will also fill out a short questionnaire to determine any familial ophthalmologic abnormalities (questions include eye problems, ophthalmic history, and risk factors for glaucoma). The most important glaucoma risk factors are high IOP and a first-degree relative having glaucoma. By completing both the screening and questionnaire, we reduce the probability that a control actually has glaucoma to less than 1%. Most other common age-related eye diseases (macular degeneration and cataract) cause a lowering of visual acuity. That is why we measure the acuity. We also make a picture of the retina that enables the discovery of glaucoma and retinal disease. If all these tests are negative, presence of a relevant eye disease is

very unlikely.

Both the patients and healthy subjects will be screened for the presence of DPOAEs and for normal middle ear function with tympanometry.

If the selection criteria are met, the subjects will then complete the experiment.

Eye screening tests:

Refraction and Visual Acuity: Measured by means of a letter chart.

Non-contact Tonometry: A pulse of air will be used to assess the subjects* eye pressure, without any physical contact. A raised intraocular pressure is one indicator of glaucoma.

Optical Coherence Tomography: A short scan that uses light to take cross-sectional images of the retina will be used to screen for glaucoma.

A screening visual field examination: This test is performed after the subject has placed his/her chin on the chin rest. A series of weak light stimuli are projected onto a bowl-shaped background in which the patient/subject has to press a button when he/she sees the stimulus. The stimuli vary in intensity and position in the bowl. This test is performed to rule out field of view defects.

Corneal Pachymetry: This test is performed to determine central corneal thickness, which is influenced by IOP. A small probe is gently placed on the front of the eye (cornea) to measure the thickness. This test is part of the routine Glaucoma patient visits.

Procedures:

After the screening, subjects who meet the inclusion criteria will have their blood pressure will be taken.

Next, the subjects will undergo two auditory tests in the ENT department.

DPOAEs: In this test, a small earpiece (similar to an MP3 player earphone) will be inserted in the subject*s ear that will present 2 tones at specified levels (at about the level of a vacuum cleaner, not loud enough to cause any damage) and frequencies. This device will measure the DPOAEs in the subjects.

Ear absorbance: A small earpiece will be inserted in the subject*s other ear. It will be presented a continuous tone in different frequencies (from 0.25kHz to 8 kHz) and air pressure from - 600 daPa to 300 daPa. This device will measure the absorbance curve of the ear.

These two tests will be performed in 7 body positions: 90, 45, 30, 20, 10, 0, -10, -20 degrees (assuming a horizontal of 0). DPOAEs (Elios Echodia Device) and ear absorbance (Titan Interacoustics) will be measure simultaneously (one earpiece in each ear) at each position, that mean at the same time. In the upright and -20 degree position they will be measured after allowing 45 seconds to reach a steady state in ICP, while in the supine position they will remain for 15 minutes before measurements are taken. In the other positions changes from one to another will be spend around 30 seconds, to allowed the normalization of the emissions.

IOP will be measured simultaneously with the two auditory tests using a handheld tonometer.

The tilt table (Design approved by to the Terzake Deskundige) will have ankle straps to safely secure the subject.

Study burden and risks

Patients and healthy subjects will have one visit to the ENT and ophthalmology departments to perform the screening tests and if selected, the experiment. Healthy subjects will undergo a routine screening test in the ophthalmology department to rule out the presence of glaucoma. Screening in the ENT department will take place for patients and healthy subjects and will include assessment of any middle ear problems and a test to detect the presence or absence of DPOAEs. If abnormal eye screening results are obtained for healthy subjects, they will be referred to their GP, as will be the case for ear abnormalities in all participants. Detection of signs of an eye or ear condition may cause psychological stress, however, an early diagnosis will allow treatments to be initiated and therefore more preservation of visual or hearing functioning. Glaucoma patients will not perform any ophthalmological screening tests; therefore there is no risk of identifying any other eye conditions. Subjects who meet the selection criteria will then undergo the ear absorbance and DPOAE testing. The tests are non-invasive but they will be tilted on a table, which may cause minimal discomfort. Patients will spend 15 minutes for reception, additional questions, and screening and, if they meet the selection criteria, 30 minutes for the experiment. The total time will therefore be about 1 hour. Healthy subjects will require 30 extra minutes for the eye screening, which will make their total participation time 1.5 hour.

Contacts

Public
Universitair Medisch Centrum Groningen

Hanzeplein 1 30001 Hanzeplein 1 30001
Groningen 90700 RB
NL
Scientific
Universitair Medisch Centrum Groningen

Hanzeplein 1 30001 Hanzeplein 1 30001
Groningen 90700 RB
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- 50-75 years of age
- Presence of DPOAEs and tympanometry in at least one ear
- Group 1: Upright IOP of 21mmHg or lower (determined during the screening test)
- Group 2: Diagnosed Glaucoma, upright IOP of 21mmHg or lower with or without IOP lowering treatment, and established disease progression rate based on perimetry
- Sign the informed consent.

Exclusion criteria

- Poor condition of both middle ears during the tympanometric test
- No presence of DPOAEs
- Abnormality of the middle ear or external auditory canal (sequelae of ear infections, cerumen, sequelae of intervention on the tympanic membrane).
- For healthy controls, any eye disease or family history of glaucoma. This will be determined by form F1 and the ophthalmologic screening described in section 2 of C1 (reseach protocol).

Study design

Design

Study type:	Observational non invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Basic science

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	60
Type:	Anticipated

Ethics review

Approved WMO

Date:	08-04-2019
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL64980.042.18