Evaluating retinal blood flow autoregulation by means of Optical Coherence Tomography Angiography (OCT-A)

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Observational non invasive

Summary

ID

NL-OMON47772

Source
ToetsingOnline

Brief title
Autoregulation of retinal blood flow

Condition

- Other condition
- Glaucoma and ocular hypertension
- Vascular hypertensive disorders

Synonym
Glaucoma;POAG

Health condition

Vascular hypotensive disorders

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 Uitzing

Intervention

Keyword: Autoregulation, Blood Pressure, OCT-Angiography, Retina

Outcome measures

Primary outcome

Optic disc capillary density, macula capillary density, and arteriole diameter

(assessed by OCT-A) as a function of blood pressure. The calculation of these

parameters is based on custom MATLAB software that will be applied on the

images.

Secondary outcome

N/A

Study description

Background summary

Glaucoma is an eye disease in which degeneration of retinal ganglion cells results in the loss of the visual field and - if left untreated - blindness.
The concept of an elevated intraocular pressure (IOP) as the only cause of glaucomatous damage is nowadays considered outdated or at least incomplete, since some people develop glaucoma without an increase in IOP (normal-tension glaucoma [NTG]).
The existence of NTG has resulted in the vascular hypothesis of glaucoma, which focuses on the perfusion of the optic nerve head (ONH) and retinal nerve fiber layer (RNFL). Indeed, epidemiological studies found associations between low systemic blood pressure and longstanding hypertension and glaucoma. However, a blood pressure measurement alone does not reflect ocular perfusion reliably in

individual patients. Therefore, a different approach is needed in order to better address ocular perfusion.
Optical Coherence Tomography-Angiography (OCT-A) is a recent method developed to obtain images of the retinal microvasculature with a scanning protocol that is no different to a regular OCT scan. The novelty lies within the software*s incorporated algorithm which uses the decorrelation between consecutive B-scans to generate angiographic images in a matter of seconds. Contrary to the current gold-standards (Fluorescein and Indocyanine Angiography), OCT-A is non-invasive. What*s more, it presents excellent repeatability and reproducibility. By incorporating OCT-A in our study we aim to get a more accurate evaluation of perfusion by looking directly to the retina.
Arterioles in the retina are characterized by their intrinsic ability to autoregulate by changing their diameter in response to external stimuli such as variations in blood pressure. This mechanism is useful in maintaining a constant blood flow and, thus, constant oxygen supply in the retina. However, autoregulation fails if the blood pressure is either too low or too high.
A common issue that occurs when trying to interpret the results of vascular deficiency in glaucoma is the *chicken-egg* problem. A reduced blood flow could be either the cause or the result of thinning of the retinal nerve fiber layer (RNFL). For this reason, we have decided to first include only non-glaucomatous subjects coming from the full BP range because, in order to unravel the association between blood pressure and perfusion, it is necessary to first evaluate the findings of OCT-A in a healthy (that is, non-glaucomatous) population.
Three aspects are of particular importance:
1) that the population should cover the extremes of blood pressure values.
2) that a subset of individuals presents symptoms associated with autonomous and/or autoregulatory dysfunction (migraine, cold intolerance, orthostatic hypotension).
For this reason a subset of this population (cold intolerance) and an equal number of healthy controls will be evaluated for vasoconstriction after a cold-provocation test has taken place (Referentie: B.D. Salmenson, J. Reisman, S.H. Sinclair, D. Burge. Macular capillary hemodynamic changes associated with Raynaud's phenomenon. Ophthalmology, 99 (6) (1992), pp. 914-919)
3) that we address both early-stage untreated, and long-standing treated hypertension (each autoregulatory curve might have different properties).

Study objective

The objective of this study is to compare OCT-A findings between five groups of non-glaucomatous subjects characterised respectively by a) low symptomatic, b) low asymptomatic, c) normal asymptomatic, d) untreated high asymptomatic, and e) treated high blood pressure. Ocular blood flow, autoregulation of the retinal vessels and RNFL thickness will be addressed.

Study design

This is a cross-sectional, observational study. Expected duration is 6-8 months. Subjects who responded to our advertisement receive the information letter and the informed consent form. They also fill out a short questionnaire concerning their ophthalmic medical history. After informed consent is obtained, subjects will visit the Laboratory of Experimental Ophthalmology (LEO) where initially the screening procedure will take place. This will include:
•Blood Pressure measurement in sitting position using a standard electronic device (Omron K6 comfort)
•Visual Acuity and Refraction: using a standardized letter chart
•Non-contact Tonometry: A pulse of air will be used to assess the subject*s eye pressure, without any physical contact. A raised intraocular pressure is an indicator of glaucoma.
•Frequency Doubling Perimetry: Visual fields will be assessed for scotomata using the C20-1 Frequency Doubling Perimetry test. Subjects will place their head on a chin-rest and will look into a hemispheric bowl. Weak flickering sinusoidal gratings will be shown at 17 different locations within the bowl (corresponding to different locations in the visual field) and subjects will be asked to press a button if they see the stimulus. This will enable identification of any visual field defects.
Screening is expected to last approximately 20 minutes. The reasoning behind it is binary. On the one hand, we wish to exclude any eye disease (other than simple refractory abnormalities) which will perhaps interfere with OCT-A image quality (e.g. cataract). On the other hand, this study is designed strictly for non-glaucomatous subjects for the reasons that have already been covered in previous sections. The aforementioned tests are used in routinely glaucoma screening. The eye is not touched during the screening.
All eligible subjects will then be asked to remove their contact lenses (if applicable) and 1% tropicamide (mydriatic) drops will be applied to both eyes. Pupil dilation is necessary because optimal image quality is crucial to the project. During the 20-minute waiting time for pupil dilation, subjects will be asked to fill one short medical history questionnaire including questions designed to detect a cluster of symptoms related to vascular or autonomic abnormalities. In addition, we will record each subject*s Body Mass Index (BMI) by simply measuring their weight and height.
Documentation of the retinal and vessel health will be recorded via fundus photography with a Topcon fundus camera: the subjects are instructed to put their chin on the chin-rest, and then they see a flash of light that might dazzle them for only a few seconds. Two photos of the retina will be taken from each eye.
Next, the subject will be asked to place their head on a chin-rest in front of the OCT system (Canon HS-100) and to focus on a fixation cross. Two regular pictures of each eye will be taken, one of the fovea and one of the optic nerve head. These images will show the thickness of the subjects retina. Thinning of the retina is indicative of glaucoma. Subsequently, two more pictures of each

eye will be taken using the angiographic module. Importantly, OCT-A (as well as any OCT module) is an entirely noninvasive technique: it determines blood flow from differences in light reflectance in consecutive images. An image is a matter of <3 seconds for OCT and <10 seconds for OCT-A. The patient will be kindly instructed not to blink during each scan. Since image artifacts considerably hamper the study, it is possible that some of the OCT and OCT-A measurements will be repeated. For this reason we expect this part of the protocol to last up to 15 minutes (5 minutes for fundus photography and 10 minutes for OCT scans).
For the second part of the protocol, the subject will rest in supine position for 5 minutes before being asked to stand for another 3 minutes in order to assess orthostatic hypotension. Blood pressure as well as heart rate will be recorded using the same device in both positions. OCT-A images will be immediately obtained from both eyes in the same way they were obtained before. If the subject belongs to group #1c (cold intolerance, see section 4.1) then this part of the protocol will not be performed. Instead, a cold pressor test will take place: subjects will immerse their hands in cold water (0-4°C) for 2 minutes or less if they feel uncomfortable. Blood pressure and heart rate will also be recorded at the end of the procedure and OCT-A images will again be immediately obtained. The cold pressor test will also be performed on an equal number of randomly selected controls from group 3 (see section 4.1). This part of the protocol is expected to last approximately 20 minutes. Hence, the whole procedure, taking the arrival of the patient in the LEO as starting point, is expected to last less than 90 minutes including instructions and a short break.

Study burden and risks

OCT-A imaging uses only light and does not pose a risk to the subjects. Subjects are required to place their chin on a chinrest and focus on a cross, trying not to blink during each scan. Scanning duration is less than 10 seconds. 1% Tropicamide is commonly used in a clinical setting before an OCT scan to improve the quality of the images. Ophthalmological examinations that will be performed during screening do not differ from standard tests performed on every new patient who enters the ophthalmology clinic. During the ophthalmologic examination no contact will be made with the eye. Lastly, even though detection of signs of an eye condition that the subject was unaware of may affect the individual negatively, an early diagnosis is overall beneficial.

Contacts

Public
Universitair Medisch Centrum Groningen

Hanzeplein 1

Groningen 9713GZ
NL
Scientific
Universitair Medisch Centrum Groningen

Hanzeplein 1
Groningen 9713GZ
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

subjects between 50 and 65 years;- Group #1: Symptomatic low blood pressure individuals
Defined as having at least one of: systolic blood pressure below 98 mmHg or diastolic blood pressure below 58 mmHg (without the use of any antihypertensive treatment), and at least one of:
a) migraine:
Migraine is defined as already diagnosed, or a score of 4 or 5 in the corresponding section of the questionnaire, according to the Migraine Screening Questionnaire.
b) orthostatic hypotension:
Orthostatic hypotension is defined as already diagnosed, or a sustained reduction of systolic blood pressure (SBP) of at least 20 mmHg or diastolic blood pressure (DBP) of 10 mmHg within 3 minutes of standing.
c) cold intolerance:
Cold intolerance is defined as a score of 30 or more in the corresponding section of the questionnaire.;- Group #2: Asymptomatic low blood pressure individuals
Defined as having at least one of: systolic blood pressure below 98 mmHg or diastolic blood pressure below 58 mmHg (without the use of any antihypertensive treatment), and none of the symptoms described in Group #1.;- Group #3: Asymptomatic normal blood pressure individuals
Defined as having systolic blood pressure between 113 and 143 mmHg, and diastolic blood

pressure between 67 and 85 mmHg (without the use of any antihypertensive treatment), and none of the symptoms described in Group #1.;- Group #4: Asymptomatic untreated high blood pressure individuals
Defined as having at least one of: systolic blood pressure above 158 mmHg or diastolic blood pressure above 94 mmHg, not using any antihypertensive treatment, and having none of the symptoms described in Group #1.;- Group #5: Treated high blood pressure individuals
Defined as having systolic blood pressure below 135 mmHg and diastolic blood pressure below 79 mmHg, together with a medical history of hypertension and the use of any antihypertensive medication for at least the past 1 year.

Exclusion criteria

•visual acuity less than 0.8
•intra-ocular pressure more than 21 mmHg
•any visual field defect
•sphere of more than (+/-)3D or cylinder of more than (+/-)2D
•positive family history (father, mother, brother or sister) of glaucoma
•OCT-A image quality of 6 or less
•pathological fundus photographs
•diagnosed diabetes mellitus of any type
•medical history of cerebrovascular disease, heart disease or severe anemia

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:	Recruitment stopped
Start date (anticipated):	22-11-2017
Enrollment:	125
Type:	Actual

Ethics review

Approved WMO Date:	18-09-2017
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	11-06-2018
Application type:	Amendment
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	NL61508.042.17
Other	UMCG Register (201700322) and NTR (NTR6444)