Physiological Stress 15O-H2O Total-body PET/CT protocol

Published: 27-02-2023
Last updated: 04-01-2025

The primary objective:Study the feasibility of physiological stressors and their effect in myocardial perfusion 15O-H2O Total-body PET/CT with stress adenosine as a reference in healthy volunteers and in CAD patients.The secondary objectives:1....

Ethical review	Approved WMO
Status	Pending
Health condition type	Coronary artery disorders
Study type	Observational invasive

Summary

ID

NL-OMON53400

Source
ToetsingOnline

Brief title
Physiological Stress Total-body PET/CT

Condition

- Coronary artery disorders

Synonym
coronary artery disease, myocardial perfusion

Research involving
Human

Sponsors and support

Primary sponsor: Nucleaire Geneeskunde en Moleculaire Beeldvorming
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: 15O-H2O, Coronary Artery Disease, Physiological stressors, Total-body PET/CT

Outcome measures

Primary outcome

The main parameters to measure are regional and global MBF and CFR during rest and stress with the different proposed stressors: adenosine, breath-holding manoeuvre, Valsalva manoeuvre and bicycle exercise.

MBF will be calculated by a research dedicated software (Carimas) in ml/g/min based on 15O-H2O Total-body PET/CT acquisitions.

CFR will be calculated as the ratio of stress MBF and rest MBF.

CFR=(stress MBF)/(rest MBF)

Data of myocardial perfusion will be analysed to address the feasibility of breath-holding manoeuvre, Valsalva manoeuvre and bicycle exercise as stress myocardial perfusion test during 15O-H2O Total-body PET/CT. Adenosine stress serves as the reference method.3330

Final values in these parameters will be reported for all the cohorts in a descriptive manner:

-Normally distributed quantitative variables will be presented with mean, standard deviation and 95 % confidence interval.

-Non-normally distributed data will be presented with median and interquartile range.

Secondary outcome

The secondary parameters will be measured by rest and stress phases (with adenosine stress and with the different proposed stressors: breath-holding manoeuvre, Valsalva manoeuvre and bicycle exercise):

• CBF is the blood volume that flows per unit per mass per unit in time in brain tissue calculated by a software (PMOD) and expressed in ml/g/min based on 15O-H2O Total-body PET/CT acquisitions.

• RBF and SBF refer to the blood volume that flows to the kidneys and to the spleen respectively. These measurements are expressed in ml/g/min and will be calculated using dedicated software (PMOD) based on 15O-H2O Total-body PET/CT dynamic images.

Quantitative descriptive analysis will be performed to report the performance of CBF, RBF and SBF in rest and during physiological and adenosine stress.

Study description

Background summary

In the department Nuclear Medicine and Molecular Imaging of the UMCG, a traditional clinical protocol for cardiac quantitative perfusion starts with a Computed Tomography (CT) transmission scan. Subsequently, the rest image acquisition using Positron Emission Tomography (PET) is initiated directly

after an injection of 400 MBq of 15O-H2O, lasting in total 5-6 minutes. Then, 10 minutes of delay must be held for 15O-H2O decay before acquisition of the stress phase. The last consists in the administration of 140 µg /kg/min of adenosine infusion, followed after 2 minutes by an injection of 400 MBq of 15O-H2O, and finally, the acquisition of stress images by a second PET scan that lasts 5-6 minutes.
At present, only pharmacological stressors can be used for the stress phase of a Myocardial Perfusion Imaging (MPI) PET, mainly due to the characteristics of the radiotracers. Since these radiotracers have a short half-life time, this does not allow for the performance of physiological stressors outside the PET/CT camera.

Several physiological stressors have been proposed for the acquisition of stress images on different modalities of perfusion imaging, including breathing manoeuvres, increased intrathoracic pressure or Valsalva manoeuvre and bicycle exercise.

Breathing manoeuvres are based on the O2 and CO2 response. CO2 is a recognized vasodilator of myocardial blood vessels that leads to changes in myocardial oxygenation. Several studies have assessed and validated a breathing-manoeuvres-stress-protocol consisting of hyperventilation for 60 seconds followed by breath-holding for 15 to 60 seconds. It has been reported that elevated levels of PaCO2 can cause myocardial hyperaemia at the same extent as adenosine. However, it is important to highlight that all these results were demonstrated with cardiac magnetic resonance imaging (MRI) and taking only anatomical and functional parameters into account, while perfusion parameters were lacking. It must be emphasized that breathing manoeuvres are safe and well-tolerated with only transient symptoms reported such as headache and dizziness. Additionally, it is easier to perform, and patients remain in total self-control. Another advantage is the lower cost, and also that the stress procedure can be reversed rapidly within 2-3 breaths.

Valsalva manoeuvre consists of a persistent exhalation with a closed glottis for 20 seconds, with the aim of increasing the intrathoracic pressure to 20-40 mmHg. This manoeuvre triggers an autonomic response in blood pressure, heart rate and blood flow. In studies performed with MRI to investigate heart and brain function and perfusion, the Valsalva Manoeuvre has been proposed and evaluated in comparison with stressors such as acetazolamide injection, breathing CO2 and breath holding. It has been reported in brain MRI that performing a Valsalva manoeuvre for 5 seconds produces a similar effect as breath-holding for 20 seconds.

Regarding exercise as stressor, a cycling ergometer compatible with MRI was created in the early 2010. This ergometer was developed for cardiac MRI to study the left ventricular function and structure by avoiding the use of dobutamine. However, cardiac MRI lacks the quantitative information regarding Myocardial Blood Flow (MBF) and Coronary Flow Reserve (CFR).

For 15O-H2O PET, there is only one study available that compared bicycle exercise against adenosine stress. The authors concluded that it seems feasible to use a supine ergometer as physiological stressor in this imaging modality, however, the sample size was quite small (i.e. 10 patients) and consisted only of healthy volunteers, so the consistency of these outcomes in patient groups still needs to be studied.

The rationale of Total-body PET was already constructed in 2000, whereas the first pilot studies were performed in 2018. This new technology enables a longer follow-up time of the radiotracer with less noise and lower radiation dose. Furthermore, one of the main advantages of this modality within the research field is that it allows for simultaneous imaging of multiple organs. Based on this last benefit, the blood flow towards organs which are related to the heart will also be evaluated (i.e. brain, kidneys and spleen).

The presence of heart disease has been linked to the onset of impairments in other major organs (i.e. brain, kidney, spleen), and parallel, primary dysfunctions in these organs have also been demonstrated to impact the prognosis regarding cardiovascular health. Regarding brain-heart interactions, an association between Coronary Artery Disease (CAD) and the incidence of ischemic stroke and/or ischemic transitory attack has been demonstrated. The other way around, depression, anxiety and other brain disorders have been proven to impact the overall prognosis in CAD patients. Furthermore, a link between CAD and the cognitive domain was found with MRI, evidenced by CAD patients that had a significantly decreased Cerebral Blood Flow (CBF) relative to healthy controls. However, further research with more sensible techniques such as PET/CT is needed to enlighten the possible relation between heart and brain perfusion.

With respect to kidney-heart interactions, it has been described that elderly CAD patients have a higher prevalence of reduced renal function when compared with younger patients (i.e. diminished estimated-Glomerular Filtration Rate). As a matter of fact, patients with CAD have an increased risk of developing chronic kidney disease. Furthermore, when the stage of renal insufficiency is reached in patients with CAD, it increases their risk of major adverse cardiovascular events.

Finally, regarding heart-spleen interactions, less links have been proposed, but some interesting associations have been theorized. In a preclinical study, it was found that the Splenic Blood Flow (SBF) was prioritized in settings of decreased cardiac output. More recently, SBF was showed to behave similar to myocardial blood flow (MBF) in patients undergoing Cold Pressor Stress (CPS). Lastly, splenic switch-off (i.e. visible decrease in splenic signal intensity during adenosine stress as compared to rest) has been proposed as a tool to evaluate the success/failure of the adenosine-induced MBF response.

However, the underlying physiological phenomena responsible for these

interactions remain unclear. Moreover, objective evidence regarding the changes that each of these organs undergo in response to alterations in the other in terms of perfusion status and organ-blood flow has not been documented.

Study objective

The primary objective:
Study the feasibility of physiological stressors and their effect in myocardial perfusion 15O-H2O Total-body PET/CT with stress adenosine as a reference in healthy volunteers and in CAD patients.

The secondary objectives:
1. Explore the measurement and associated blood flows in the connected organs brain, kidneys and spleen to the heart.
2. Obtain the information regarding the subjects experience with each of the proposed physiological stressors. For this, a symptom questionnaire was developed to be addressed at the end of the protocol.

Study design

It is a feasibility study, which will assess the effect of physiological stressors in myocardial perfusion using 15O-H2O Total-body PET/CT with conventional adenosine stress as a reference in healthy volunteers and patients with CAD.

This study will be carried out with the Biograph Vision Quadra scanner in the UMCG, the Netherlands.

Study burden and risks

The two non-investigational products used in this protocol (i.e.15O-H2O and adenosine) are registered products used within indication.
However, the main risk of this protocol is the ionizing radiation. This can cause cancer which manifests itself after many years or decades. The estimated associated risk of developing fatal cancer is proportional to the dose and also to the participant*s age at the time of exposure. The risk for younger people is higher than for older people and the risk for females is higher than for males of the same age. The Total Research Protocol Dose (TRPD) quoted for each cohort are in addition to standard clinical care. According to report 26 of the Netherlands Commission on Radiation Dosimetry, radiation exposure of this study is allowed to be in category 2b at most. All participants in this study will receive a maximum of 200 MBq per IV administration of 15O-H2O, with a total radiation effective dose of 1.1 mSv for 15 healthy volunteers and 0.88 mSv for 5 CAD patients. The 15 healthy volunteers who will perform the complete protocol will receive an additional dose of 1.0 mSv from the ultra-low-dose CTs, whereas the 5 CAD patients who will get 4 scans will receive an additional

dose of 0.8 mSv from the ultra-low-dose CTs, based in Tin Filter technology which is available and already has been used in our department previously. Therefore, the total radiation dose of the complete protocol is 2.1 mSv (5 scans). The total radiation dose of the protocol with 4 scans is 1.68 mSv. The radiation dose for healthy volunteers will be 2.1 mSv meanwhile, the radiation dose for the CAD patients is 1.68 mSv with this protocol. Since total radiation exposure in this study is 2.1 mSv, males must be at least 10 years old and females must be at least 20 years old to fall into category 2b.

Contacts

Public
Selecteer

Hanzeplein 1
Groningen 9713GZ
NL
Scientific
Selecteer

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

o Healthy subjects:
* Aged above 40 years

* Male or female
* Good general health
* Height 1.60 m - 1.85 m
* BMI 20-25 kg/m2
* Informed consent signed

o Patients suspected or known with Coronary Artery Disease:
* Aged above 40 years
* Male or female
* Height 1.60 m - 1.85 m
* Diagnosed or suspected with Coronary Artery Disease
* Informed consent signed

Exclusion criteria

o Healthy subjects:
* Clinical history of diabetes, hypertension, dyslipidemia
* History of cardiac disease
* Family history of Coronary Artery Disease
* Active or short history of cigarette smoking
* Inability or unwillingness to give informed consent
* Known hypersensitivity to adenosine
* Clinical active bronchospasm
* Chronic obstructive pulmonary disease or asthma
* Chronic kidney disease
* Expressed willing to not continue with the participation
* Pregnancy or breastfeeding
* Claustrophobia
* Not able to cycle

o Patients suspected or known with Coronary Artery Disease:
* Known hypersensitivity to adenosine
* Bundle branch block
* Presence or temporal or definitive pacemaker
* Presence of heart valve prosthesis, shoulder prosthesis, prosthetic reconstruction of the chest
wall or other prosthetic devices within the field of view
* Clinical active bronchospasm
* Chronic obstructive pulmonary disease or asthma
* Expressed willing to not continue with the participation
* Pregnancy or breastfeeding
* Claustrophobia
* Not able to cycle

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	20-04-2023
Enrollment:	20
Type:	Anticipated

Ethics review

Approved WMO

Date:	27-02-2023
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Not approved

Date:	14-11-2024
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	NL81215.042.23