Monocyte behaviour in human upon sympathetic stimulus via LBNP with and without beta-blocker therapy.

Published: 14-06-2013
Last updated: 22-04-2024

ObjectivesPrimary: 1. To evaluate the feasibility of observing monocyte behaviour in humans in healthy controls upon sympathetic stimulus via LBNP. Secondary: 2. To evaluate the effect of inhibiting the nervous signalling pathway via inhibition of...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Arteriosclerosis, stenosis, vascular insufficiency and necrosis
Study type	Observational invasive

Summary

ID

NL-OMON38648

Source
ToetsingOnline

Brief title
LBNP

Condition

- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
Atherosclerosis, vessel wall inflammation

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Atherosclerosis, Cardiovascular disease, LBNP device, Monocytes

Outcome measures

Primary outcome

Main study parameter

1. Changes in monocyte count and differentiation after LBNP in healthy volunteers

Secondary outcome

Secondary study parameters

2. Changes in monocyte count and differentiation after LBNP in splenectomized patients or patients with advanced cardiovascular disease.

3. Differences between monocyte behaviour and characteristics in healthy volunteers, splenectomized patients and patients with advanced cardiovascular disease.

4. Suppression of monocyte release via inhibition of nervous signaling pathway via B receptor blockade.

Study description

Background summary

In tandem with our increasing insight of atherosclerotic inflammation, the immune system has gained interest as a therapeutic target for cardiovascular diseases. However, targeting of for example monocytes and macrophages and their *detrimental* functions without compromising the host defense first requires an increased knowledge of the kinetics and fate of these cells in human. Recently, Nahrendorf et al demonstrated in mice that myocardial infarction and stroke can

accelerate atherosclerosis through a systemic inflammatory response. Also, there is an extreme rapid and abundant monocytosis continuously sustained by the spleen via sympathetic nervous system signaling through the *3-adrenoceptor, both in the acute as chronic phase. So far, most data on immune response and immunocyte kinetics is investigated in mice. Although these principles could apply to the human immune response, direct translation from mouse studies is problematic; the mouse immune system is well understood and readily manipulated, however, it also diverges in many ways from that of humans. Therefore, whenever possible, findings in mice should be paralleled by human clinical studies. In this respect lower body negative pressure (LBNP) is a method to induce acute stress to otherwise healthy subjects. LBNP results in pooling of blood in the lower body and a consequent reduction in central blood volume. This acute stress imposed by loss of central blood volume gives rise to complex neurocirculatory (eg sympathetic nerve system) and humoral reflexes that attempt to compensate for this loss and to ensure the continued perfusion of the heart and brain. Thus, using LBNP we could possibly mimic the sympathetic nervous system signaling pathway for the release of monocytes in human.
Here, we propose to increase our knowledge of the kinetics of monocytes in humans. We have designed our study in several steps. As the first step we propose to study in vivo monocyte characteristics in healthy volunteers after a sympathetic stimulus with LBNP. Next, we can evaluate the contribution of the spleen by interfering with the beta3 signalling by selectively inhibiting via betablockade. If proven feasible, we propose as the second step to repeat this study in splenectomized patients and patients with advanced cardiovascular disease.

Study objective

Objectives

Primary:
1. To evaluate the feasibility of observing monocyte behaviour in humans in healthy controls upon sympathetic stimulus via LBNP.
Secondary:
2. To evaluate the effect of inhibiting the nervous signalling pathway via inhibition of the beta receptor on the monocyte characteristics and behaviour in healthy volunteers.
3. To evaluate differences monocyte characteristics and behaviour upon sympathetic stimulus via LBNP in healthy controls, splenectomized patients and patients with advanced cardiovascular disease off and on beta blockers.

Study design

Design

This study will be conducted in several phases.

Step 1 * LBNP in healthy volunteers
* Step 1a * LBNP in healthy volunteers.
* Step 1b * LBNP after initiation of betablocker therapy

Step 2 * LBNP in patients with cardiovascular disease and splenectomized patients before and after initiation of betablocker therapy.

Study burden and risks

The results of this study contribute to the development of our understanding on the roll of immune system in humans. Also, it contributes to the development of novel anti-inflammatory directed atherosclerotic treatment strategies. Patients receive no direct benefits. Risks associated with participation are related to either LBNP procedure or B blocker therapy. During LBNP procedure the patient and vital signs are continuously observed. In case of impending cardiovascular collapse or per request of the subject, negative pressure can immediately be terminated by the subject or attending physician. Beta blocker therapy is a generally well accepted drug, of which we do not expect serious side effects in two weeks treatment.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Healthy controls
* Adults (either gender) * 18 years
* Willing and able to participate in study protocol;Splenectomized patients
* Adults (either gender) * 18 years
* History of traumatic splenectomy
* Participated in scientific research at the AMC previously and have given permission via informed consent to be willing to be contacted for other research at the AMC in the future.
* Willing and able to participate in study protocol;Cardiovascular patients
* Adults (either gender) * 18 years
* Cardiovascular patients are recognized by atherosclerotic cardiovascular disease, thus atherosclerosis in either coronary, carotid, aortic and/or peripheral arteries. The above needs to be documented in the history of the patient by one or more of the following:
o History of coronary heart disease (angina pectoris, myocardial infarction), cerebrovascular disease (stroke), peripheral arterial disease (claudicatio intermittens).
o Objective diagnostic (imaging) examinations, including exercise treadmill test, stress echocardiography, myocardial perfusion scintigraphy, right or left common carotid intima-media thickness (CIMT) by ultrasound > 75th percentile by American Society of Echocardiography, presence of carotid plaque by carotid ultrasound (focal thickening > 50% or CIMT > 1.5 mm), coronary artery calcium score > 100 Agatston units in patients < 60 years of age, CT or conventional coronary or peripheral angiography with at least one moderate or severe luminal stenosis, CT coronary angiography with one or more atherosclerotic plaques demonstrating positive remodeling or hypodense plaque morphology, moderate or severe aortic atherosclerosis by CT or Transesophageal echocardiography,
o History of revascularization procedure (e.g., coronary or peripheral arterial bypass grafting, percutaneous coronary or peripheral intervention, carotid endarterectomy).
* Willing and able to participate in study protocol
* For patients using statins, angiotensin-converting enzyme (ACE) inhibitors (ACE-I) or angiotensin-receptor blockers (ARBs), non-statin lipid-modifying therapy, thiazolidinediones, inhaled steroids, or leukotriene modifying agents; use of a stable dose for at least 6 weeks prior to the first visit.

Exclusion criteria

Healthy controls are not eligible if they meet one of the criteria listed below:
* Any known systemic chronic disorders/medical condition or chronic use of systemic

medication that could interfere with the conduct of the study in the opinion of the investigator.
* Inability or unwillingness to comply with the protocol requirements, or deemed by investigator to be unfit for the study.;Splenectomized patients are not eligible if they meet one of the criteria listed below:
* History of cardiovascular diseases (including atherosclerotic CVD, heartfailure, etc) or cardiovascular medication such as use of beta blocker therapy, calciumantagonists and CYP2D6 inhibitors.
* Auto-immune disease/vasculitis, other active inflammatory diseases, proven or suspected bacterial infections. Recent (<1 month prior to screening) or ongoing serious infection requiring IV antibiotic therapy that could interfere with the conduct of the study in the opinion of the investigator.
* Known systemic disorders such as asthma, hepatic, renal, hematologic, and malignant diseases or any clinically significant medical condition that could interfere with the conduct of the study in the opinion of the investigator.
* Inability or unwillingness to comply with the protocol requirements, or deemed by investigator to be unfit for the study.;Cardiovascular patients are not eligible if they meet one of the criteria listed below:
* Other cardiovasular disease than the previously defined atherosclerotic cardiovascular disease patients, including heart failure, cardiomyopathy, aneurysms, hypertensive heart disease, cor pulmonale, cardiac dysrhythmias including sick-sinussyndrome, 2nd- en 3rd degree AV-block, inflammatory heart disease such as endocarditis, myocarditis and rheumatic heart disease, valvular heart disease and congenital heart disease.
* Use of beta blocker therapy, calciumantagonists and CYP2D6 inhibitors (for example paroxetin, fluoxetin) within 3 months prior to screening visit are not allowed based on their effect on bloodpressure regulation.
* Auto-immune disease/vasculitis, other active inflammatory diseases, proven or suspected bacterial infections. Recent (<1 month prior to screening) or ongoing serious infection requiring IV antibiotic therapy that could interfere with the conduct of the study in the opinion of the investigator.
* Known systemic disorders such as asthma, hepatic, renal, hematologic, and malignant diseases or any clinically significant medical condition that could interfere with the conduct of the study in the opinion of the investigator.
* Inability or unwillingness to comply with the protocol requirements, or deemed by investigator to be unfit for the study.

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled

Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	30
Type:	Anticipated

Ethics review

Approved WMO

Date:	14-06-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC

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	NL45015.018.13