Dutch Limb Suspension 2006

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Primary objectiveTo identify specific genes in the NO pathway that are turned on or off by inactivity. The results will disclose key-genes in the NO pathway relevant for vascular adaptations. Secondary objectiveTo correlate functional vascular...

Ethical review	Approved WMO
Status	Pending
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON30048

Source
ToetsingOnline

Brief title
DLS '06

Condition

- Other condition

Synonym
inactivity

Health condition

inactiviteit: risicofactor voor atherosclerose

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Nederlandse Hartstichting

Intervention

Keyword: cardiovascular diseases, gene-expression, inactivity, vascular function

Outcome measures

Primary outcome

Expression of specific genes in the NO pathway (mRNA).

Secondary outcome

Functional vascular characteristics as blood flow and systolic and diastolic vessel diameter of the carotid artery, the brachial artery and the superficial femoral artery; flow mediated dilation (FMD) and dilation due to nitroglycerine (NMD) of the susperficial femoral artery; dilation after infusion of ACh and L-NMMA of the superficial femoral artery. Additionally, muscle function parameters as muscle force, rate of muscle force rise, relaxation time and muscle fatigue and bone function.

Study description

Background summary

Physical inactivity is an important and independent risk factor for atherosclerosis and cardiovascular and a numerous additional amount of other chronic health conditions. According to extensive scientific results, it is evident that inactivity has a great influence on the structural and functional vascular parameters in humans, which are (in)directly linked to cardiovascular morbidity and mortality. To gain further insight in the factors that initiate these vascular adaptations, we have to search for the specific underlying genes that are responsible for the NO pathway regulation resulting in these vascular changes. Deficient physical activity in the current sedentary culture has been shown to lead to abnormal gene expression. The present project will combine human in vivo and in vitro research to identify the key genes in the NO pathway responsible for vascular adaptations to inactivity and training in humans. The current project will be the first to identify genes in the NO pathway that are turned on or off by inactivity in humans and that are related to vascular

adaptations. Our results will initiate follow up studies in which these key-genes will be knocked out in animal models or by specific drugs in humans to further delineate the relevance and redundancy of those genes. Understanding the genetic mechanisms leading to inactivity-related cardiovascular disease may contribute to more adequate prevention strategies of these diseases.

Study objective

Primary objective
To identify specific genes in the NO pathway that are turned on or off by inactivity. The results will disclose key-genes in the NO pathway relevant for vascular adaptations.
Secondary objective
To correlate functional vascular adaptations to inactivity with transcriptome analyses (achieved in the primary objective). The results will reveal specific genes linked with vascular adaptations to either inactivity.

Study design

To achieve these objectives, healthy subjects will immobilize one leg for three weeks. Muscle biopsy of the vastus lateralis and the gastrocnemius will be taken before and after immmobilisation to provide information on gene expression. The vascular parameters will be measured by echo Doppler ultrasound and plethysmography by experienced vascular nurses. The NO pathway will be manipulated by infusion of Ach (stimulates NO synthase) and L-NMMA (blocks NO synthase). Functional vascular adaptations will be measured in parallel to gene expression profiling in order to correlate the vascular functional data and the transcriptome characterization. Additionally, musculo-skeletal function will be evaluated.

Intervention

The intervention consists of 3 weeks of immobilisation of one leg. This will be done by elevation of the active foot by a sole and fixing of the foot by belts to the upper body, in a way the foot does not touch the ground. During immobilisation, the subject will walk on crutches and the limb will not be loaded.

Study burden and risks

Using the immobilisation method described in this protocol, only a part of the leg is immobilized, while the joints remain flexible. Except for small ankle oedema for the first days, a relatively colder skin of the suspended leg and a small, but controlable risk of thrombosis, no side-effects have been reported. After the restart of the normal loading, good recovery was present at the suspended leg and the effect of immobilisation will disappear in some weeks

according to literature. The canulation of the femoral artery can lead to a light hematoma or some bleeding afterwards. The subjects are controled for this very precisely. The medication is infused only locally in doses at which no systemic effects are expected, based on comparable studies. Considering the removal of the muscle biopt samples, the upper leg might be a bit stiff and sensitive afterwards. In very rare cases, a light hematoma can occur, that will disappear after some days. All tests are performed extensively on the participating departments, without any complications.

Contacts

Public
Academisch Medisch Centrum

Geert Grooteplein 21
6525 EX Nijmegen
Nederland
Scientific
Academisch Medisch Centrum

Geert Grooteplein 21
6525 EX Nijmegen
Nederland

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Man
2. Aged 18-30 jr

3. Healthy (to own saying)
4. Non smoker
5. BMI >19 and <25 kg/m2
6. Signed informed consent

Exclusion criteria

1. Performing sports for over 5 hours a week
2. Hypertension (DBP>90, SBP>140)
3. Increased level of D-Dimer in blood plasma
4. Physical condition preventing measurement of maximal oxygen consumption
5. Recent fracture of a limb
6. Cardiovascular, musculo-skeletal, metabolic, hormonal or chronic diseases
7. Use of medication with possible hemodynamic effects
8. History of medical or surgical events that might have any influence on the results

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-06-2006
Enrollment:	10
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Not available
Generic name:	Acetylcholine
Product type:	Medicine

Brand name:	Not available
Generic name:	NG-monomethyl-L-arginine (L-NMMA, remmer NO synthase)

Ethics review

Approved WMO Date:	19-06-2006
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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
EudraCT	EUCTR2006-001253-93-NL
CCMO	NL11400.091.06