# External Surface Cooling In huMan endOtoxemia

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To determine the effects of fever control with external cooling during LPS-induced endotoxemia on:1. host immune response2. coagulation processes 3. tissue perfusion and oxygenation4. neurovascular coupling

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|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Bacterial infectious disorders |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON45163

**Source**
ToetsingOnline

**Brief title**
ESCIMO

### Condition

- Bacterial infectious disorders

**Synonym**
endotoxemia, Sepsis

**Research involving**
Human

### Sponsors and support

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

## Intervention

**Keyword:** endotoxemia, fever, normothermia, volunteers

## Outcome measures

### Primary outcome

A significant decrease in plasma Il-6 levels

### Secondary outcome

Other markers of

1. host immune response

2. coagulation

3. tissue perfusion and oxygenation

4. neurovascular coupling

# Study description

### Background summary

Experimental animal data and preliminary clinical data suggest that septic patients with fever may benefit from fever control with external cooling, presumably via inhibition of excessive inflammation. However, the mechanisms of this treatment modality remain to be determined in humans. Also, there are safety concerns regarding fever control in sepsis, as cooling may induce immunosuppression, coagulopathy, and may impair circulation. In healthy individuals, lipopolysaccharide (LPS) causes a reversible endotoxemia, including fever, tachypnea, tachycardia and hypotension. These physiologic and metabolic changes approximate those in human sepsis, making this model ideal for an in depth study of mechanisms of external cooling as well as examining safety. We will use this model to assess the effects of fever control (36°C) using external cooling on the host immune response, coagulation and circulation.

### Study objective

To determine the effects of fever control with external cooling during LPS-induced endotoxemia on:

1. host immune response
2. coagulation processes
3. tissue perfusion and oxygenation
4. neurovascular coupling

**Study design**

Healthy volunteers will be screened (medical history, physical examination, ECG, blood examination) by a physician. On study day, all subjects (n=24) will be injected with LPS 2ng/kg i.v., which results in chills at 2 hours and fever spiking at 3-4 hours. Using external cooling devices, Group 1 (n=6) will be kept at normothermia (36°C) from start of experiment. 3 hours after LPS infusion (coinciding with the temperature peak due to LPS), group 2 (n=6) will be cooled to 36°C. The control group will not be cooled. The study will end 8 hours after LPS infusion. A group will only recieve LPS + medication

Study timeline:
A pilot study will be performed with 1 subject (group 1). If the study design is deemed feasible, we will continue with groups 1 + 3. After which, an interim analysis will be performed on our primary endpoint (IL-6) and hemodynamic parameters such as blood pressure. If no benefit is seen in the intervention group, group 2 will not be studied. An additional group will recieve only LPS + medication

Cooling: Subjects will be cooled using a cooling management system also used for cardiac arrest patients. This system cools externally using 4 gelpads located on the back, thorax, abdomen and upper legs. These gelpads are connected to the machine which in turn keeps the pads a the wanted temperature. Also, cold NaCl will be given to reach target temperature and if necessary 1g acetaminophen

Temperature measurement: A rectal temperature probe will be placed to provide feedback to the external cooling device.

Shivering: To counteract shivering in the cooled group, counter skin warming will be done of the hands and feet using an adapted Bair Hugger, which flows warm air over desired area. Also, to counteract shivering, buspirone (30mg), pethidine (max 600mg) or clonidine (75mcg bolus and max infusion rate 2mcg/kg/h), magensium sulfate (max 9g).
Sampling: Blood will be taken before LPS infusion and at 1,3,6,8 hours for hematology, parameters of immune host response and coagulation tests. Hemodynamics will be monitored by arterial catheter, arterial blood gas, echocardiography, and by imaging of the microcirculation.

**Intervention**

Group 1: LPS + medication + external cooling to 36°C from T = 0 hours after LPS infusion
Group 2: LPS + medication+ external cooling to 36°C from T = 3 hours after LPS infusion
Group 3: LPS
Group 4: LPS + medication

**Study burden and risks**

Benefits: none
A dose of 2ng/kg LPS in healthy volunteers has proven to be safe in previous studies at this institution. Cooling healthy, awake volunteers has also been proven to be safe, even to temperatures well below the proposed 36°C in this study.
Although the combination of external cooling and LPS has not been performed before, we do not expect this to cause safety issues. Discomfort is expected to be mainly related to shivering, which will be treated immediately. A (relative) bradycardia will occur, reduction in cardiac output is variable, but if this occurs, it will result in normalization of a hyperdynamic circulation. Electrolyte disorders as seen during hypothermia are not expected.
Pethidine, clonidine, buspirone and magnesium sulfate have been given to healthy volunteers being cooled to suppress shivering without problems, at higher doses given than in this study. As the intervention lasts only 8 hours, there is no risk of toxicity, even though cooling could decrease metabolism.
From a safety perspective subjects will be monitored during the total experiment and until 2 hours afterwards.

# 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

1. Healthy male volunteer
2. Age >= 18 years <35 years
3. BMI 20-25

## Exclusion criteria

1. No informed consent
2. Any abnormal test result during the screening prior to inclusion of the study (medical history, physical examination, ECG, blood examination).
3. History of drug abuse
4. Any present medication use on prescription
5. Participation in any other medical drug study < 3 months
6. Participation in previous volunteer studies using LPS
7. History of an allergic reaction to opiates

# Study design

## Design

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|---|---|
| Study type: | Interventional |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Open (masking not used) |

**Primary purpose:** Treatment

### Recruitment

NL

| | |
|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 10-05-2017 |
| Enrollment: | 24 |
| Type: | Actual |

## Ethics review

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|---|---|
| Approved WMO Date: | 14-10-2016 |
| Application type: | First submission |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 17-05-2017 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 12-09-2017 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 07-12-2017 |
| Application type: | Amendment |
| 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

ID: 24451
Source: Nationaal Trial Register
Title:

## In other registers

| Register | ID |
|---|---|
| CCMO | NL53460.018.15 |
| OMON | NL-OMON24451 |