# the influence of remote ischemic preconditioning on inflammation during human endotoxemia, a pilot proof-of-principle study

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To determine the effect of RIPC of the upper limb on the inflammatory response during human endotoxemia (infusion of LPS), as well as the additional effect of 7-day RIPC compared with single-dose RIPC.

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

## Summary

### ID

NL-OMON42617

**Source**
ToetsingOnline

**Brief title**
RISPENDO

### Condition

- Autoimmune disorders
- Ancillary infectious topics

**Synonym**
auto-immune diseases, infectious diseases

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Intensive Care
**Source(s) of monetary or material Support:** Ministerie van OC&W

## Intervention

**Keyword:** Endotoxemia, Inflammation, Remote ischemic preconditioning

## Outcome measures

### Primary outcome

The main study endpoint is the difference in circulating TNF-* over time following LPS administration between the multiple-dose RIPC group and the control group (see section 10 for details on the statistical comparisons).

### Secondary outcome

Secondary study parameters/endpoints

* Other circulating cytokines (including, but not limited to IL-6, IL-10 and IL-1RA)

* Body temperature

* Hemodynamic parameters (heart rate, blood pressure)

* Leukocyte counts and differentiation

* Plasma adenosine levels and expression of adenosine receptors and enzymes involved in adenosine metabolism in leukocytes

* Presence of TLR ligands in plasma (HEK cells)

* HSP70 levels in plasma

* HIF-1* expression in leukocytes

* Production of inflammatory mediators by ex vivo-stimulated leukocytes

* Inflammatory transcriptional pathways (by use of qPCR/microarrays/RNA

sequencing)

# Study description

### Background summary

In a wide range of auto-inflammatory and infectious diseases attenuation of the immune response could be beneficial. Remote ischemic preconditioning (RIPC) has been identified as a means of protecting patients undergoing cardiac surgery from perioperative myocardial ischemic damage. This protection can be divided in a `first window of protection` directly after preconditioning and a `second window` that protects patients 12-48 hour after preconditioning. Repeated RIPC might have additional value, possibly by combining beneficial effects of the first and second windows of protection. The mechanisms behind these effects are under investigation, but attenuation of the inflammatory response is a major candidate. However, this has not yet been demonstrated in the setting of systemic inflammation in humans in vivo. This study aims to investigate the effects of (repeated) ischemic preconditioning on inflammation during human endotoxemia.

### Study objective

To determine the effect of RIPC of the upper limb on the inflammatory response during human endotoxemia (infusion of LPS), as well as the additional effect of 7-day RIPC compared with single-dose RIPC.

### Study design

A parallel randomized controlled pilot study in healthy male volunteers during experimental endotoxemia. Subjects will be randomized to either:
1. The multiple-dose RIPC group (n=10): a group of 10 subjects that will receive 4 cycles of remote ischemic preconditioning of the upper limb per day in the 7 consecutive days before the endotoxemia experiment. The last dose will be applied 40 minutes before LPS administration.
2. The single-dose RIPC group (n=10): a group of 10 subjects that will receive a single RIPC dose, starting 40 minutes before LPS administration.
3. The control group (n=10): a group of 10 subjects that will be administered LPS without RIPC.

### Intervention

A blood-pressure cuff with handheld rubber inflation balloon and manometer is placed on the non-dominant arm of the subject. The cuff will be placed proximally from the elbow with the most proximal part of the cuff placed in the

armpit. The cuff will be inflated to 250 mmHg after which a 5 minute countdown is started. After 5 minutes the pressure is released and the 5 minute countdown for reperfusion is started. This concludes one cycle out of a total of four.

1 *RIPC-dose* consists of 4 cycles of 5 minute ischemia followed by 5 minute reperfusion as described above.

**Study burden and risks**

The burden of the study procedures consists of two visits to the hospital for the single-dose RIPC and placebo groups:
* A screening visit of approximately 1 hour in which a medical interview, physical examination and a blood withdrawal by vena puncture will be carried out.
* The endotoxemia experiment day, on which the subjects will be hospitalized for approximately 10 hours. An arterial line for hemodynamic monitoring and blood sampling will be placed under local anesthesia using 2% lidocaine. A venous cannula will be placed for intravenous fluid infusion.

Subjects in the multiple-dose RIPC group will visit the hospital 8 times. The screening visit (1 hour) and endotoxemia experiment day (10 hours) are the same as for the single-dose RIPC and placebo group. On the 6 days preceding the experiment day the subjects in the multiple-dose RIPC group will visit the hospital 6 times for 35 minutes. Subjects will receive a blood pressure cuff that is inflated to 250 mmHg of pressure for 5 minutes and is deflated for 5 minutes before being inflated again (see for detailed description section 5.1)

The subjects will not benefit directly from participation to the study. A subject fee is provided which is slightly higher for subjects in the multiple-dose RIPC group. A structured risk assessment is provided in section 13. We feel that the risk to, and burden for the subjects are in proportion to the potential value of the research.

# Contacts

**Public**
Selecteer

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**Scientific**
Selecteer

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# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

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

## Inclusion criteria

Age *18 and *35 yrs
Male
Healthy

## Exclusion criteria

Use of any medication
Smoking
Use of recreational drugs within 21 days prior to endotoxemia experiment day
Use of caffeine or alcohol within 1 day prior to endotoxemia experiment day
Previous participation in a trial where LPS was administered
Surgery or trauma with significant blood loss or blood donation within 3 months prior to endotoxemia experiment day
Participation in another clinical trial within 3 months prior to endotoxemia experiment day
History, signs, or symptoms of cardiovascular disease
History of frequent vaso-vagal collapse or of orthostatic hypotension
History of atrial or ventricular arrhythmia
Hypertension (RR systolic>160 or RR diastolic>90)
Hypotension (RR systolic<100 or RR diastolic<50)
Conduction abnormalities on the ECG consisting of a 1st degree atrioventricular block or a complex bundle branch block
Renal impairment: plasma creatinine>120 µmol/L
Liver function abnormality: alkaline phosphatase>230 U/L and/or ALT>90 U/L

History of asthma
Obvious disease associated with immune deficiency
CRP > 20 mg/L
WBC> 12x109/L or clinically significant acute illness, including infections, within 4 weeks before endotoxemia day

# Study design

## Design

| | |
|---|---|
| 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): | 29-10-2015 |
| Enrollment: | 30 |
| Type: | Actual |

## Medical products/devices used

| | |
|---|---|
| Generic name: | sphygmomanometer |
| Registration: | Yes - CE intended use |

# Ethics review

Approved WMO

| | |
|---|---|
| Date: | 21-10-2015 |
| 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 |
|---|---|
| Other | Clinical Trials.gov - nummer volgt |
| EudraCT | EUCTR2015-002099-25-NL |
| CCMO | NL53584.091.15 |