# A randomised, single blinded, prospective, observational study of molecular biological effects of xenon inhalation used for early preconditioning in humans undergoing coronary artery bypass grafting

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The aim of this study is to evaluate cardio-protective effects of xenon inhalation in humans and to identify enzymes contributing to cardio-protection influenced by xenon in patients scheduled for CABG surgery.

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| **Ethical review** | Approved WMO |
| **Status** | Pending |
| **Health condition type** | Coronary artery disorders |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON31122

**Source**
ToetsingOnline

**Brief title**
A study on effects of xenon inhalation in humans undergoing CABG; part II

### Condition

- Coronary artery disorders

**Synonym**
CABG

**Research involving**

Human

## Sponsors and support

**Primary sponsor:** Erasmus MC, Universitair Medisch Centrum Rotterdam
**Source(s) of monetary or material Support:** Ministerie van OC&W

## Intervention

**Keyword:** CABG, molecular biological effects, Xenon

## Outcome measures

### Primary outcome

The present application of xenon seeks to investigate the mechanisms behind xenon preconditioning in humans. This will be done by examination of 3 myocardial tissue probes (called A, B and C) per patient (numbered 1, 2, 3, etc.) in a molecular laboratory setting detecting activity of PKC-e, p38MAPK, JNK and ERK. For transport purposes the probes will be preserved in Eppendorf® cups placed into liquid nitrogen (-30 °C).

### Secondary outcome

Troponin T, CPK, CPK-MB, pro-BNP and S-100 protein levels will be examined both before operation and during the first 24 hours of the ICU period after the operation.

# Study description

### Background summary

Ischaemic preconditioning describes the protection of myocardial tissue against infarction by short, non-lethal periods of ischaemia. In the last years the volatile anaesthetics, like e.g. isoflurane, have been recognized to mimic the strong cardio protection exerted by ischaemic preconditioning (pharmacological or anaesthetic induced preconditioning). Recent data indicate that also the

inert gas xenon is able to induce preconditioning of the heart in vivo. Xenon inhalation resulted in a significant reduction of the infarct size compared with controls. Calphostin C, an inhibitor of protein kinase C (PKC), and the p38 mitogen activated protein kinase (MAPK) inhibitor SB203580 abolished the preconditioning effects of xenon and isoflurane. These data suggest that PKC and p38 MAPK are key mediators of xenon-induced preconditioning. PKC-epsilon (PKC-e) is one of the isoforms present in cardiac myocytes and is mainly implicated in preconditioning mechanisms. Activation of PKC affects other downstream signalling pathways like the MAPK cascade, and in this context it has been shown that PKC-e interacts with MAPK during cardio protection. Xenon induced a significant increase of p38 MAPK phosphorylation and calphostin C abrogated this effect, demonstrating that p38 MAPK is located downstream of PKC in the signalling cascade of xenon-induced preconditioning.
These data show that xenon induces cardio protection by preconditioning and that activation of PKC-e and its downstream target p38 MAPK are central molecular mechanisms involved. Xenon activates MAPKAPK-2 and HSP-27 downstream of PKC and p38 MAPK and these data link preconditioning by xenon to the actin cytoskeleton. Although these data suggest some steps of the signal transduction cascade, the end-effectors of preconditioning mediating the cardio protective effect remains to be elucidated.
The present application seeks to investigate whether the identified enzymes of xenon-induced preconditioning play a role in a clinical setting of myocardial ischaemia. Xenon should be given shortly before aortic cross clamping in patients scheduled for coronary artery bypass surgery. Protein modifications should be correlated to clinical cardio-protective effects of xenon measured by troponin T and pro-BNP levels. To investigate whether clinical neuro-protective effects may occur at the same time, also the level of S-100 protein will be measured and patients will be asked to fill in neuro-cognitive questionnaires.

## Study objective

The aim of this study is to evaluate cardio-protective effects of xenon inhalation in humans and to identify enzymes contributing to cardio-protection influenced by xenon in patients scheduled for CABG surgery.

## Study design

This study is designed as a randomised single blinded prospective observational study. In this combined clinical-laboratory investigation with collaboration between the Thorax centre of ErasmusMC, Rotterdam and the Laboratory of Experimental Intensive Care and Anaesthesiology (LEICA) of Academic Medical Centre, Amsterdam, a total number of 20 patients per group, giving 60 patients totally will be enrolled.

## Intervention

Group A will receive in a 1 block period of 15-min: 65% xenon together with 35% oxygen,
Groep B will receive in 3 blocks of 5-min per block with an intercept of 5 min between the blocks: 65% xenon together with 35% oxygen,
Groep C will receive a 1 block period of > 10-min of 100% oxygen.

**Study burden and risks**

non applicable

## 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

Age range: 18 years or older
Patients who have to undergo elective cardiac surgery (CABG with or without valve surgery)
Written informed consent
All inclusion criteria must be met; otherwise the patient cannot be enrolled into the study

### Exclusion criteria

Age range: < 18 years
Emergency operations
Pregnancy
Severe COPD
Informed written consent missing
SaO2 < 90% (room atmosphere)
Presumed non-cooperatives
Legal incapacity
Any clinical condition which does not justify study participation in the investigator's opinion

## Study design

### Design

**Study type:** Interventional

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| Masking: | Single blinded (masking used) |
| Control: | Uncontrolled |
| Primary purpose: | Treatment |

### Recruitment

NL

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|---|---|
| Recruitment status: | Pending |
| Start date (anticipated): | 01-10-2007 |
| Enrollment: | 60 |
| Type: | Anticipated |

### Medical products/devices used

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|---|---|
| Product type: | Medicine |
| Brand name: | Xenon |
| Generic name: | Xenon |

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| Registration: | Yes - NL outside intended use |

## Ethics review

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| Approved WMO Date: | 16-10-2007 |
| Application type: | First submission |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 14-02-2008 |
| Application type: | First submission |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |

## 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 | EUCTR2007-005323-16-NL |
| CCMO | NL18865.078.07 |