Noble gases in anaesthesia practice

Dr. Layth Al tmimi MD, PhD student
Cardiovascular Anaesthesiologist
University Hospitals Leuven
Anaesthesia and outcome

- Postoperative morbidity and mortality still high
- Perioperative hypoxia/ischaemia and reperfusion (IRI)
- Negative inotropic effects
- Vasodilation and hypotension
- Postoperative complications → ↑LOS and ↑costs
Development of anaesthesia

- Monitoring
- ICU and surgical devices
- Anaesthesia medications?
Development of anaesthesia

Anaesthesia medications

- Propofol 1986
- Early 90s desflurane and sevoflurane
- Sugammadex approved for use in the Europe on July, 2008
- Noble gas: Xenon

Wenker O: Review of Currently Used Inhalation Anesthetics; Part I. The Internet Journal of Anesthesiology 1999; Vol3N2: http://www.ispub.com/journals/IJA/Vol3N2/inhal1.htm; Published April 1, 1999; Last Updated April 1, 1999.
Why noble gases
Why noble gases

- Noble gases have organ protective effects
- Xenon, Helium and Argon
- Helium and Argon have protective properties but not at physiological pressure level
Why noble gases

Medical uses of helium

- Helium use in magnetic resonance imaging (MRI)
- Helium usage in lung function testing
- Helium insufflation for laparoscopy
- Insufflation gas in Intra-arterial Balloon Pumps (IABP)
- Helium and plasma technology in surgery

Why noble gases

Xenon

- Xenon has anaesthetic (and analgesic?) effects
- Approved for ASA I-II
- Xenon is devoid of negative inotropic effects
- Xenon does not affect myocardial blood flow
- Xenon causes significantly less sympathicolysis

What are the evidences
- History of xenon
- Properties of xenon
- Xenon: mechanism of action
- Organ protective effects of xenon
- Disadvantages of xenon
- Xenon studies in UZ Leuven
- Summary and future research
History of xenon

- Sir W. Ramsay 1894-1898
- Xenon = stranger
- Trace noble gas (86 ppb)

- 1946: Laurence: narcotic effects of xenon in mice
- 1950: Cullen and Gross: narcotic effects of xenon in humans

Lawrence JH et al: J Physiol (Lond) 1946;105:197-204.
History of xenon

- Properties of xenon
- Xenon: mechanism of action
- Organ protective effects of xenon
- Disadvantages of xenon
- Xenon studies in UZ Leuven
- Summary and future research
Properties of xenon

- 1965 Eger E.: MAC = 71%
- 2001 Nakata: MAC = 63%
- 1973 Blood gas solubility coefficient 0.14
- 1998 Blood gas solubility coefficient 0.11

<table>
<thead>
<tr>
<th></th>
<th>Blood/gas PC</th>
<th>MAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrous oxide</td>
<td>0.47</td>
<td>104</td>
</tr>
<tr>
<td>Halothane</td>
<td>2.3</td>
<td>0.74</td>
</tr>
<tr>
<td>Isoflurane</td>
<td>1.4</td>
<td>1.15</td>
</tr>
<tr>
<td>Sevoflurane</td>
<td>0.69</td>
<td>2.05</td>
</tr>
<tr>
<td>Desflurane</td>
<td>0.42</td>
<td>6.0</td>
</tr>
</tbody>
</table>

Properties of xenon

Emergence and early cognitive function in the elderly after xenon or desflurane anaesthesia: a double-blinded randomized controlled trial†

M. Coburn¹ * #, J.-H. Baumert¹ #, D. Roertgen¹, V. Thiel¹, M. Fries¹, M. Hein¹, O. Kunitz¹, B. Fimm² and R. Rossaint¹

Table 5 Emergence from anaesthesia. All time points are presented in minutes as mean and lower and upper 95% confidence intervals in parentheses

<table>
<thead>
<tr>
<th>Time</th>
<th>Desflurane</th>
<th>Xenon</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>To open eyes</td>
<td>8.1 (6.3–9.9)</td>
<td>4.8 (3.9–5.7)</td>
<td>0.001</td>
</tr>
<tr>
<td>To react on demand</td>
<td>8.6 (6.7–10.6)</td>
<td>4.9 (3.7–6.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>To extubation</td>
<td>8.9 (6.6–11.2)</td>
<td>4.9 (3.9–5.8)</td>
<td>0.001</td>
</tr>
<tr>
<td>To time and spatial orientation</td>
<td>10.8 (8.7–13.0)</td>
<td>7.4 (6.1–8.8)</td>
<td>0.007</td>
</tr>
</tbody>
</table>
Properties of xenon

NEUROSCIENCES AND NEUROANAESTHESIA

aeplex monitor for the measurement of hypnotic depth in patients undergoing balanced xenon anaesthesia

C. Stoppe†, D. Peters†, A. V. Fahlenkamp, J. Cremer, S. Rex, G. Schälte, R. Rossaint and M. Coburn*  
Department of Anaesthesiology, RWTH University Hospital, Pauwelsstr. 30, D-52074 Aachen, Germany
Properties of xenon

- Xenon is an inert gas → no metabolism
- No hepatic or renal clearance
- Recovery time does not depend on duration of anaesthesia

Properties of xenon

- NOT FLAMMABLE
- NON TOXIC

Malignant hyperthermia

Not teratogene
- History of xenon

- Properties of xenon
  - Xenon: mechanism of action
  - Organ protective effects of xenon
  - Disadvantages of xenon

- Xenon studies in UZ Leuven

- Summary and future research
Xenon: mechanism of action

Most inhalation agents

GABA<sub>A</sub> Receptors (inhibiting brain cell firing)

Xenon

NMDA Receptors (causing brain cell firing)

Xenon: mechanism of action

Xenon inhibits NMDA receptors in cultured rat hippocampal neurons.

History of xenon

Properties of xenon

Xenon: mechanism of action

- Organ protective effects of xenon
- Disadvantages of xenon
- Xenon studies in UZ Leuven

Summary and future research
Organ protective effects of xenon

- CNS
- Cardiovascular system
- Kidneys
- Other organs?
Xenon and CNS
Xenon and CNS

Xenon reduces neurohistopathological damage and improves the early neurological deficit after cardiac arrest in pigs*

Michael Fries, MD; Kay Wilhelm Nolte, MD; Mark Coburn, MD; Steffen Rex, MD; Anne Timper, MS; Kai Kottmann, MS; Katharina Siepmann, MS; Martin Häusler, MD; Joachim Weis, MD; Rolf Rossaint, PhD

Figure 1. S-100 protein serum levels in control and xenon (Xe)-treated animals. CPR, cardiopulmonary resuscitation; BL, baseline; PR, minutes postresuscitation.

Figure 2. Neurologic deficit score (NDS) after cardiopulmonary resuscitation in control and xenon (Xe) treated animals. †p < 0.01 vs. Control; *p < 0.05 vs. Control.

The neuroprotective effects of xenon and helium in an *in vitro* model of traumatic brain injury*

Mark Coburn, MD; Mervyn Maze, MB, FRCA, FMedSci; Nicholas P. Franks, PhD, FMedSci
Xenon Pretreatment May Prevent Early Memory Decline after Isoflurane Anesthesia and Surgery in Mice

Marcela P. Vizcaychipi¹, Dafydd G. Lloyd¹, Yanjie Wan², Mark G. Palazzo¹, Mervyn Maze³, Daqing Ma¹*

Conclusion
Xenon exposure immediately prior to surgery prevents early memory decline in mice
Xenon and cardiovascular system
Xenon and cardiovascular system

Multicenter Randomized Comparison of Xenon and Isoflurane on Left Ventricular Function in Patients Undergoing Elective Surgery

Frank Wappler, M.D.,* Rolf Rossaint, M.D.,† Jan Baumert, M.D.,‡ Jens Scholz, M.D.,§ Peter H. Tonner, M.D.,§ Hugo van Aken, M.D.,‖ Elmar Berendes, M.D.,‖ Jan Klein, M.D.,# Diederik Gommer, M.D.,** Alfons Hammerle, M.D.,†† Andreas Franke, M.D.,‡‡ Thomas Hofmann, M.D.,§§ Jochen Schulte am Esch, M.D.,||

for the Xenon Multicenter Study Research Group###

• n = 259

Conclusion

• Xenon in contrast to isoflurane devoid of negative inotropic effects
Xenon and the cardiovascular system

SHOCK, Vol. 34, No. 6, pp. 628–635, 2010

**XENON/REMIFENTANIL ANESTHESIA PROTECTS AGAINST ADVERSE EFFECTS OF LOSARTAN ON HEMODYNAMIC CHALLENGES INDUCED BY ANESTHESIA AND ACUTE BLOOD LOSS**

Roland C.E. Francis,* Claudia Philippi-Höhne,† Adrian Klein,* Philipp A. Pickerodt,* Matthias S. Reyle-Hahn,‡ and Willehad Boemke*

*Department of Anesthesiology and Intensive Care Medicine, Charité-Universitätsmedizin Berlin, Campus Virchow-Klinikum and Campus Charité Mitte, Berlin; †Department of Anesthesiology and Intensive Care Medicine, Universitätsklinikum Leipzig AöR, Leipzig; and ‡Department of Anesthesiology and Intensive Care Medicine, Evangelisches Waldkrankenhaus Spandau, Berlin, Germany

- Animal study- 6 dogs
- xenon protects against circulatory side effects of losartan pre-treatment and thus may afford safer therapeutic use of losartan during acute haemorrhage.
A prospective, randomized design on 40 patients of ASA classes III and IV showed that TEE showed better LV function with xenon.
Xenon and the cardiovascular system

Fig 2 Intraoperative time course of CO (a), left ventricular stroke work index (LVSWI) (b), SV (c), and PCWP (d). Open circles indicate the xenon group; closed circles indicate the sevoflurane group. *P<0.05 vs baseline, tested by unpaired t-test. ANOVA testing for all time points did not reveal a significant change.
Xenon and the cardiovascular system

- Xenon protects against myocardial ischaemia-reperfusion injury

- Xenon delivers pharmacological preconditioning

- Xenon reduces left ventricular remodelling after myocardial infarction
  Roehl AB et al. Anesthesiology 2013; 118:1385-94
Xenon and nephroprotection
Xenon Preconditioning Protects against Renal Ischemic-Reperfusion Injury via HIF-1α Activation

Daqing Ma,* Ta Lim,* Jing Xu,† Haidy Tang,* Yanjie Wan,† Hailin Zhao,* Mahmuda Hossain,* Patrick H. Maxwell,‡ and Mervyn Maze*

*Department of Anaesthetics, Pain Medicine and Intensive Care, Faculty of Medicine, Imperial College London, London, United Kingdom; †Department of Anesthesiology, Gongli Hospital, Pudong, Shanghai, China; and ‡Division of Medicine, Rayne Institute, University College of London, London, United Kingdom

ABSTRACT
The mortality rate from acute kidney injury after major cardiovascular operations can be as high as 60%, and no therapies have been proved to prevent acute kidney injury in this setting. Here, we show that preconditioning with the anesthetic gas xenon activates hypoxia-inducible factor 1α (HIF-1α) and its downstream effectors erythropoietin and vascular endothelial growth factor in a time-dependent manner in the kidneys of adult mice. Xenon increased the efficiency of HIF-1α translation via modulation of the mammalian target of rapamycin pathway. In a model of renal ischemia-reperfusion injury, xenon provided morphologic and functional renoprotection; hydrodynamic injection of HIF-1α small interfering RNA demonstrated that this protection is HIF-1α dependent. These results suggest that xenon preconditioning is a natural inducer of HIF-1α and that administration of xenon before renal ischemia can prevent acute renal failure. If these data are confirmed in the clinical setting, then preconditioning with xenon may be beneficial before procedures that temporarily interrupt renal perfusion.

Xenon Treatment Protects Against Cold Ischemia Associated Delayed Graft Function and Prolongs Graft Survival in Rats

H. Zhao¹, H. R. Watts¹, M. Chong¹, H. Huang¹, C. Tralau-Stewart², P. H. Maxwell³, M. Maze⁴, A. J. T. George⁵ and D. Ma¹,6,*
Xenon and other organs
Xenon and Liver transplantation

Patients were remarkably stable.
• Required only moderate, temporary catecholamine support
• Xenon anaesthesia proved to be feasible
• Immediate postoperative organ function was satisfactory in all patients.
Xenon and Liver transplantation

• Xenon produces the highest regional blood flow in the brain, liver, kidney and intestine.

• Xenon causes the flow of the hepatic artery to remain stable

History of xenon

Properties of xenon

Xenon: mechanism of action

Organ protective effects of xenon

Disadvantages of xenon

Xenon studies in UZ Leuven

Summary and future research
Disadvantages of xenon

• 1 L of xenon costs approximately € 20

• “Economic mode” and closed circuit ≈ 10 l/h

• Production of 1L consumes 1 million more energy than N2O

• ↑ the incidence of PONV
Disadvantages of xenon

Incidence of postoperative nausea and emetic episodes after xenon anaesthesia compared with propofol-based anaesthesia

M. Coburn¹ *, O. Kunitz² †, C. C. Apfel³, M. Hein¹, M. Fries¹ and R. Rossaint¹ ‡

¹Department of Anaesthesiology, University Hospital Aachen of the RWTH Aachen, Pauwelsstreet 30, D-52072 Aachen, Germany. ²Department of Anaesthesia and Intensive Care Medicine, Mutterhaus der Borromäerinnen Medical Centre, Trier, Germany. ³Perioperative Clinical Research Core, Department of Anaesthesia and Perioperative Care, University of California, San Francisco, CA, USA

*Corresponding author. E-mail: mcoburn@ukaachen.de

Background. Xenon has been proved to be safe and efficacious for general anaesthesia in numerous trials. In addition, experimental studies demonstrate that xenon inhibits the 5-hydroxytryptamine type 3 (5-HT₃) receptor. As 5-HT₃ receptor antagonists are known to decrease postoperative nausea and vomiting (PONV) to an extent comparable with a propofol-based total i.v. technique, we tested the hypothesis that general anaesthesia with xenon would result in a reduced incidence of PONV similar to that observed with propofol-based anaesthesia.

Methods. After obtaining approval from the local ethics committee and written informed consent, 142 patients were randomized to receive xenon anaesthesia or propofol-based total i.v. anaesthesia (TIVA), both supplemented with remifentanil. The incidence of postoperative nausea and emetic episodes was recorded in the post-anaesthesia care unit and on the ward more than 24 h after anaesthesia.

Results. A total of 142 patients were equally distributed between the xenon and TIVA groups. Anaesthesia was maintained with mean (so) concentrations of either xenon 61 (2)% or propofol 100 (20) µg kg⁻¹ min⁻¹. Incidences of nausea and emetic episodes over the whole 24-h period were 66.2% and 35.2% in the xenon group and 26.8% and 16.9% in the TIVA group (P<0.001 and P<0.021).

Conclusion. Despite knowing the 5-HT₃ antagonistic properties of xenon, its use is associated with a higher incidence of nausea and emetic episodes compared with TIVA with propofol.
Disadvantages of xenon

Xenon Does Not Prolong Neuromuscular Block of Rocuronium

Oliver Kunitz, MD, Jan-Hinrich Baumert, MD, Klaus Hecker, MD, Thorben Beeker, MD, Mark Coburn, MD, André Zühlsdorff, MD, and Rolf Rossaint

- Prospective randomized controlled trial
- 40 patients
- ASA I-II

Conclusion
- Xenon does not prolong the neuromuscular blocking effect after a single dose of 0.6 mg/kg rocuronium

(Anesth Analg 2004;99:1398–401)
Disadvantages of xenon

- High density and viscosity → increases airway resistance at high-inspired concentrations
- Problematic in spontaneously breathing patients

- History of xenon
- Properties of xenon
- Xenon: mechanism of action
- Organ protective effects of xenon
- Disadvantages of xenon
- Xenon studies in UZ Leuven
- Summary and future research
Xenon studies in UZ Leuven

- In cardiac surgery
- In cath. lab. (congenital heart disease)
- In animal lab.
Study 1
4AP7-1
Xenon anaesthesia in patients undergoing off-pump coronary artery bypass graft surgery: a prospective, randomized controlled clinical trial (EudraCT 2012-002316-12)

Al Tmimi L., Sergeant P., Van de Velde M., Meyns B., Coburn M., Rex S.
1KU Leuven - University of Leuven, Dept of Anaesthesiology, Leuven, Belgium, 2KU Leuven - University of Leuven, Cardiac Surgery, Leuven, Belgium, 3University Hospital of the RWTH Aachen, Dept of Anaesthesiology, Aachen, Germany
Xenon anaesthesia for patients undergoing off-pump coronary artery bypass graft surgery: a prospective randomized controlled pilot trial

L. Al tmimi\textsuperscript{1}, J. Van Hemelrijck\textsuperscript{1,5}, M. Van de Velde\textsuperscript{1,5}, P. Sergeant\textsuperscript{2,5}, B. Meyns\textsuperscript{2,5}, C. Missant\textsuperscript{1,5}, I. Jochmans\textsuperscript{3,6}, K. Poesen\textsuperscript{4,7}, M. Coburn\textsuperscript{8} and S. Rex\textsuperscript{1,5,*}

Hypothesis

General anaesthesia with xenon in OPCAB-surgery is non-inferior to the established anaesthetic sevoflurane regarding intraoperative vasopressor requirements.
Study 1: Primary outcome

Total intraoperative consumption of noradrenaline that required to achieve the pre-defined haemodynamic goals:

- MAP > 70 mmHg
- HR between 55 and 80 min\(^{-1}\)
- CI ≥ 2.5 l\(\cdot\)min\(^{-1}\)\(\cdot\)m\(^{-2}\)
- SvO\(_2\) ≥ 70%
Study 1: Secondary outcomes

- Occurrence of peri- and postoperative (serious) adverse events, including MACCE’s
- Depth of anaesthesia
- Need for inotropes
- Intraoperative blood loss and fluid balance
- Occurrence of postoperative delirium
- 6-month follow-up (mortality, MACCE’s and hospital re-admission)
Study 1: Materials and Methods

**Visit 0:**
- Screening
- Inclusion
- CAM, MMSE, GDS

**Visit 1 (intraoperatively):**
- Randomization
- Hemodynamics
- BIS
- Respiratory Parameters

**Visit 2 (1h post admission ICU):**
- Hemodynamics
- Respiratory Parameters
- Routine Laboratory Parameters
- Inflammatory reaction
- SAPS, SOFA
- CAM-ICU

**Visit 3 (first morning on ICU):**

**Visit 4-7: Daily until POD 5**
- Vital Parameters
- CAM-ICU
- MMSE (d3 + d7 = Visit 8)

**Visit 8: POD 7**
- Vital Parameters
- CAM-ICU
- MMSE (POD 3)

**Visit 9: hospital discharge**
- Vital Parameters
- CAM, MMSE
- MACCE

**Visit 10: 6 months after surgery**
- Mortality/Readmission to hospital
Study 1: Results (Flowchart)

Excluded (n = 37)
- Not meeting inclusion criteria (n = 29)
  - Renal dysfunction (n = 6)
  - No Dutch proficiency (n = 4)
  - MMSE < 25 (n = 5)
  - Cardiac exclusion criteria (n = 4)
  - CVA with persistent deficits (n = 3)
  - COPD (n = 2)
  - Alcohol abuse (n = 2)
  - Others (n = 3)
- Declined to participate (n = 8)

Assessed for eligibility (n = 79)

Randomized (n = 42)

Allocated to intervention (n = 21)
- Received allocated intervention (n = 21)
- Did not receive allocated intervention (n = 0)

Xenon

Allocated to intervention (n = 21)
- Received allocated intervention (n = 21)
- Did not receive allocated intervention (n = 0)

Sevoflurane

Lost to follow-up (n = 0)
Discontinued intervention (n = 0)

Lost to follow-up (n = 0)
Discontinued intervention (n = 0)

Analysed (n = 21)
- Excluded from analysis (n = 0)

Analysed (n = 21)
- Excluded from analysis (n = 0)
Study 1: Results

- No differences in baseline and demographic data
- No differences in preoperative medications
- No differences in surgery-related data
- No differences in intraoperative fluid management
- No differences in intraoperative medications except for noradrenaline and phenylephrine consumption
Study 1: Results (Vasopressor requirements)

![Graph showing phenylephrine consumption comparison between Xenon and Sevoflurane]

- **Xenon**
- **Sevoflurane**

Phenylephrine consumption (µg) vs. Experimental Condition

- **P < 0.0001**

KU LEUVEN
Study 1: Results (Vasopressor requirements)

- Noradrenaline (µg)
  - P < 0.0001

- Xenon
- Sevoflurane
Study 1: Results (Haemodynamics)
Study 1: Results (Depth of anaesthesia)

BL = Baseline (Pre-induction), T1 = After induction of anesthesia, T2 = After sternotomy, T3 = After stabilization of the left anterior wall, T4 = After enucleation of the heart, T5 = After administration of protamine, T6 = At end of surgery
# Study 1: Results (Postoperative data)

<table>
<thead>
<tr>
<th>Postoperative Data</th>
<th>Xenon (n = 21)</th>
<th>Sevoflurane (n = 21)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noradrenaline consumption PD1 (mg)</td>
<td>5 [8]</td>
<td>8 [11]</td>
<td>0.252</td>
</tr>
<tr>
<td>Piritramide consumption PD1 (mg)</td>
<td>40 [13]</td>
<td>33 [23]</td>
<td>0.314</td>
</tr>
<tr>
<td>Duration of mechanical ventilation (h)</td>
<td>15.9 [8.9]</td>
<td>14.7 [6.7]</td>
<td>0.725</td>
</tr>
<tr>
<td>ICU LOS (h)</td>
<td>44.6 [41.9]</td>
<td>50.7 [31.8]</td>
<td>0.296</td>
</tr>
<tr>
<td>Postoperative hospital LOS (d)</td>
<td>9 [2]</td>
<td>8 [8]</td>
<td>0.939</td>
</tr>
</tbody>
</table>
Study 1: Results (Cardiac markers)

A. Troponin-T (µg \cdot L^{-1})
- BL: P = 0.816
- ICU: P = 0.217
- PD1: P = 1.000

B. CK-MB massa (µg \cdot L^{-1})
- BL: P = 0.360
- ICU: P = 0.143
- PD1: P = 0.788

Xenon vs Sevoflurane
Study 1: Results (Postoperative delirium)

P = 0.044
HR = 4.209
Study 1: Results (Neurological biomarker)

![Graph showing S100β levels in BL, ICU, and PD1 stages.](Image)
Study 1: Results

Russian athletes admit Xenon doping at Winter Olympics

Drug has same effect as outlawed EPO which boosts oxygen-carrying blood cells

The Biathlon Men’s Relay at the Laura Cross-country Ski & Biathlon Center on February 22, 2014 in Sochi, Russia. Photograph: Vianney Thibaut/Agence Zoom/Getty Images
Study 1: Results (Erythropoietin)
**Study 1: Results (SAE)**

**In-hospital**
- No differences in mortality
- No differences in other serious adverse events including MACCE’s

**Out of hospital (discharge -6 months)**
- No differences in mortality
- No differences in re-hospitalisation (incidence of MACCE’s)
Study 1: Conclusion

- Xenon anaesthesia is associated with less vasopressor requirements in patients undergoing OPCAB-surgery.

- Xenon may facilitate the intraoperative haemodynamic management of cardiac surgical patients.

- Xenon may directly or indirectly provide protection from postoperative delirium (larger study is warranted).

- Xenon is non-inferior to sevoflurane regarding other postoperative outcomes.
Study 2
Study 2: Xenon as an adjuvant to propofol anaesthesia in patients undergoing off-pump coronary artery bypass (OPCAB) surgery: a randomized controlled trial

In animal experiments, xenon exerted its organprotective effects already in sub-anaesthetic concentrations.

**Hypothesis**

Application of 30 % xenon, as an adjuvant to general anaesthesia with a target controlled infusion of propofol, is superior to general anaesthesia with propofol alone with respect to haemodynamic stability.
Study 2: Abstract presented

EACTA Annual Congress 2015

Gothenburg · Sweden · June 24 - 26, 2015
Study 2: Primary endpoint

- Intraoperative haemodynamic stability, as assessed by the individual intraoperative noradrenaline consumption
Study 2: Secondary endpoints

- Incidence of postoperative delirium
- Intraoperative SAE
- Incidence of postoperative organ dysfunction and further AE
  - Length of ICU and hospital stay
- 6-month follow-up (mortality and hospital re-admission)
Study 2: Materials and Methods

- Randomized single blinded
- Elective OPCAB-surgery

- **Group A:** xenon 30% in oxygen as an adjuvant to a target-controlled infusion with propofol
- **Group B:** a target-controlled infusion of propofol alone
Study 2: Results

Assessed for eligibility (n= 86)

- Excluded (n= 36)
  - Not meeting inclusion criteria (n = 25)
    - Renal dysfunction (n = 11)
    - No Dutch proficiency (n = 5)
    - COPD (n = 3)
    - Alcohol abuse (n = 3)
    - Others (n = 3)
  - Declined to participate (n=11)

Randomized (n= 50)

- Xenon-Propofol
  - Allocated to intervention (n= 25)
    - Received allocated intervention (n= 25)
    - Did not receive allocated intervention (n= 0)
  - Lost to follow-up (n= 0)
  - Discontinued intervention (n= 0)
  - Analysed (n= 25)
    - Excluded from analysis (n= 0)

- Propofol
  - Allocated to intervention (n= 25)
    - Received allocated intervention (n= 25)
    - Did not receive allocated intervention (n= 0)
  - Lost to follow-up (n= 0)
  - Discontinued intervention (n= 0)
  - Analysed (n= 25)
    - Excluded from analysis (n= 0)
Study 2: Results

- No differences in baseline and demographic data
- No differences in preoperative medication
- No difference in intraoperative analgesia consumption
- No differences in other intraoperative data except for
Study 2: Results (Propofol requirements)

![Graph showing propofol consumption comparison between Xenon-propofol and propofol with a significant difference, $P = 0.002$.](image-url)
Study 2: Results (Noradrenaline requirements)

![Graph showing noradrenaline requirements](image)

- **Xenon-propofol**
  - Noradrenaline (µg)
  - Range: 0 to 9100
  - Mean: 3640
  - p-value: 0.003

- **Propofol**
  - Noradrenaline (µg)
  - Range: 0 to 7280
  - Mean: 3120

The graph illustrates the difference in noradrenaline requirements between the two conditions, with a statistically significant difference indicated by the p-value of 0.003.
Study 2: Results (Noradrenaline requirements)
## Study 2: Results (Postoperative data)

### Table 3: Postoperative outcomes

<table>
<thead>
<tr>
<th></th>
<th>All patients (n = 50)</th>
<th>Xenon-Propofol (n = 25)</th>
<th>Propofol (n = 25)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU LOS (h)</td>
<td>40 [28]</td>
<td>27 [38]</td>
<td>42 [27]</td>
<td>0.705</td>
</tr>
</tbody>
</table>

Data are represented as median [interquartile range].
D = day, h = hour, ICU = intensive care unit, LOS = length of stay
Study 2: Conclusion

- Xenon with propofol was superior to propofol alone regarding intraoperative noradrenaline consumption during elective OPCAB-surgery.

- Larger studies are warranted to investigate whether this finding can be translated into superior clinical outcomes. Only then, the additional costs for xenon may be justified.
Study 3
Hypothesis
In elderly cardiac surgical patients, the use of xenon anaesthesia reduces the incidence of postoperative delirium when compared to sevoflurane anaesthesia.
**Study 3: Aims**

- To assess the incidence of postoperative delirium in elderly patients undergoing elective cardiac surgery with xenon or sevoflurane anesthesia.

- To assess the delirium free days during hospital stay between the two groups.

- To evaluate the adverse and serious adverse events in each group.
Study 3: Materials and Methods

- Randomized single blinded prospective study
- Xenon (n = 91) vs. sevoflurane (n = 91)

Inclusion criteria

- Age > 65 years
- Patient scheduled for elective heart surgery with the use of cardiopulmonary bypass (CPB)
- Dutch proficiency
Study 3: Materials and Methods

Exclusion criteria

- Intraoperative need for OLV and/or FIO$_2$ > 50%
- COPD GOLD > II
- Disabling neuropsychiatric diseases
- Presence of delirium at baseline
- Alcohol abuse
- History of stroke with residuals
- Increased intracranial pressure
**Study 3: Materials and Methods**

Fig. 1: Schematic illustrations of the study visits

**Investigator I: Visit 0 (Preoperative)**
- Screening
- Enrollment
- CAM, CCI, MMSE, IQCODE, CAGE questionnaire, Katz ADL and GDS
- Preoperative CK-MB, troponin and IL

**Investigator I: Visit 2 (1h postop) and Visit 3 (1st morning in ICU)**
- Hemodynamic and respiratory parameters
- Clinical examination
- Routine laboratory parameters
- CK-MB, Troponin and Inflammatory parameters
- SOFA, SAPS, APACHE II
- CAM-ICU and ICDSC if RASS ≥ -3
- Extubation time
- AE and SAE

**Investigator I: Visit 8 (Before hospital discharge)**
- Vital parameters
- CAM(-ICU); if CAM(-ICU) positive → DI
- MMSE and Katz ADL
- DOS

**Investigator I: Visit 9 (6 months after surgery)**
- Mortality/Readmission to hospital/MMSE/Katz ADL

**Investigator II: Visit 1 (Intraoperative)**
- Randomization
- Hemodynamic parameters
- Respiratory parameters
- BIS, NIRS, TEE
- Routine blood gas analysis

**Investigator I: Visit 4 - 7 (Daily until day 5)**
- Vital parameters
- CAM(-ICU); by positive CAM(-ICU) → DI
- DOS
- MMSE (day 3 and 5)

AE: adverse event; APACHE II: Acute Physiology and Chronic Health Evaluation II; BIS: bispectral index; CAM: Confusion Assessment Method; CCI: Charlson Comorbidity Index; DI: Delirium Index; DOS: Delirium Observation Scale; GDS: Geriatric Depression Scale; ICDSC: Intensive Care Delirium Screening Checklist; ICU: Intensive Care Unit; IL: interleukin; IQCODE: Informant Questionnaire on Cognitive Decline in the Elderly; Katz ADL: Katz Index of Activities of Daily Living; MMSE: Mini-Mental State Examination; NIRS: near infrared spectroscopy; RASS: Richmond Agitation-Sedation Scale; SAPS: Simplified acute physiology score; SOFA: Sequential Organ Failure Assessment Score; SAE: serious adverse events; TEE: transesophageal echocardiography.
- History of xenon
- Properties of xenon
- Xenon: mechanism of action
- Organ protective effects of xenon
- Disadvantages of xenon
- Xenon studies in UZ Leuven
- Summary and future research
Summary and future research

Xenon

- Ideal gas properties
- Excellent haemodynamic profile
- May have neuro and nephroprotective properties
- Has cardioprotective properties

But

- Routine use?
- Cost – effectiveness
Summary and future research

- Xenon in patients undergoing TAVI?
Summary and future research

- Xenon and Liver transplantation
- Xenon and kidney transplantation
- History of xenon
- Properties of xenon
- Xenon: mechanism of action
- Organ protective effects of xenon
- Disadvantages of xenon
- Xenon studies in UZ Leuven
- Summary and future research