Potential of Volatile Anesthetics in Organ Transplantation

ISAP 2018, San Fransisco

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Disclosures

Vapor-2 is funded by:

- The Astellas European Foundation Transplantation Grant 2014
- Astellas Pharma
- Baxter/ESA grant on improvement of perioperative outcome 2017

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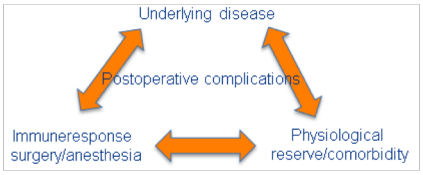
Perioperative medicine

- Surgical care: operation and the disease being treated with this operation
- Groccot-Pearse BJA 2012[1]: Response to surgery is the primary disease process and the consequent organ dysfunction the condition to focus on
- Khuri Ann Surg 2005[2]: 105,951 patients, 8 different procedures
  - Most important determinant of long-term survival: occurence of 1 of the 22 predefined postoperative complications first 30 days after surgery.



- Intra-operative interventions reduce incidence of postoperatieve complications

1. Grocott MP, Pearse RM. Perioperative medicine: the future of anesthesia? Br J Anaesth. 2012; 108(5):723-6
2. Khuri SF, Henderson WG, DePalma RG et al. Determinants of long-term survival after major surgery and the adverse effect of postoperative complications. Participants in the VA National Surgical Quality Improvement Program. Ann Surg 2005; 242:326-41

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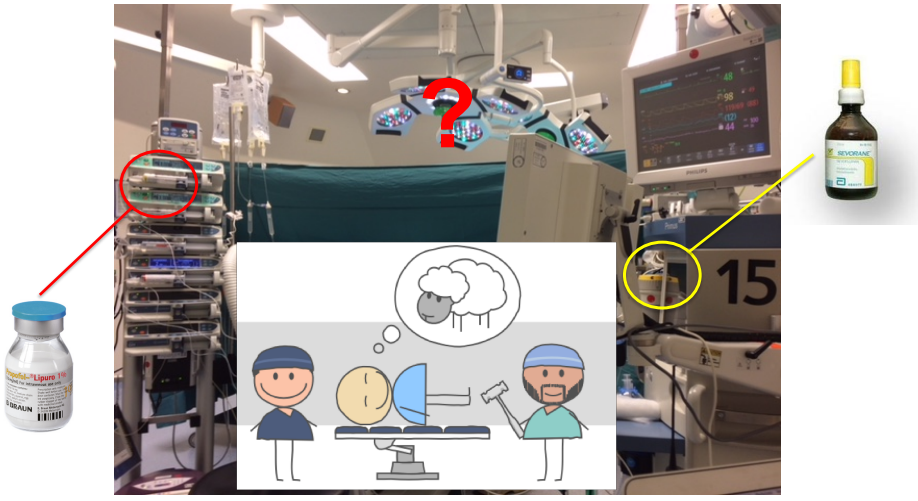

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Pleiotropic effects anesthetics

- Effects other than providing general anesthesia
- Not new
  - Gaylord/Simpson 1911
  - Graham 1916
- Increased interest in choice of anesthetics and outcome of the patient
  - Cognitive effects
  - Immunomodulation
  - **Ischemia and reperfusion injury (IRI)**

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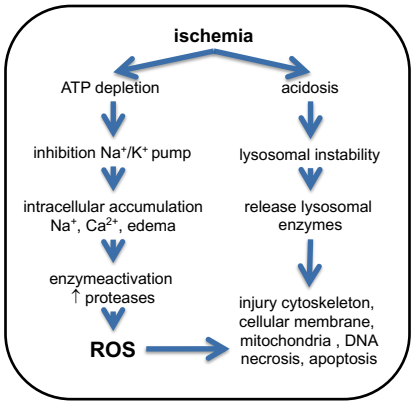
Ischemia



Nieuwenhuijs-Moeke G.J. Peroperative renal protective strategies in kidney transplantation, PhD thesis, 2018

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Ischemia:

Cell damage - Cell death

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What happens when you turn on the oxygen….

Ischemia

Reperfusion

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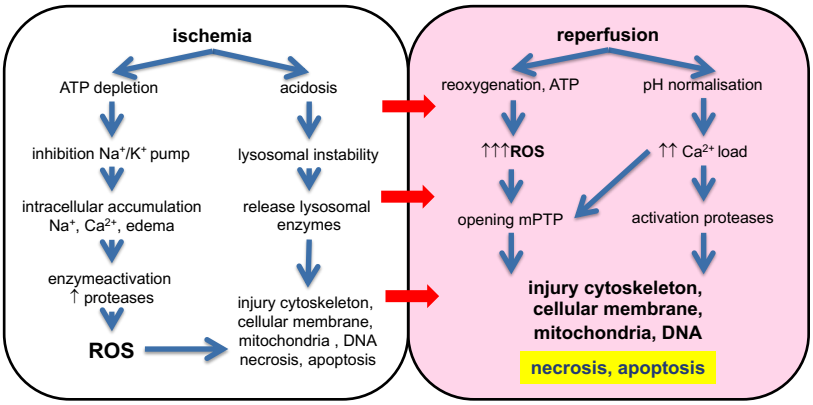
Ischemia and Reperfusion



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Reperfusion:

More cell damage - cell death ….

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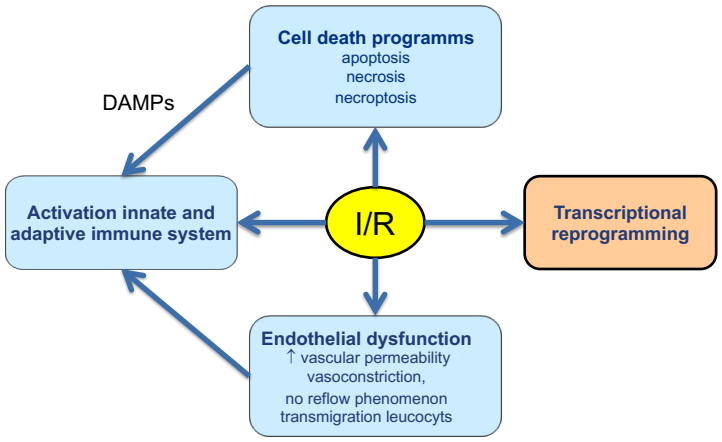
Ischemia and reperfusion injury



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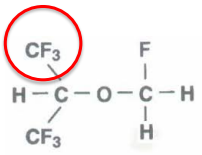
Anesthetic conditioning

- Ability of anesthetic agents to induce biochemical changes that may attenuate IRI
- Pre-, per-, postconditioning
- Mostly described for volatile anesthetics (VA)
- Trifluorohaloginated carbon (CF3) groups[1]
- Mechanism complex, multiple pathways involved



Sevoflurane

1. Urner M, Limbach LK, Herrmann IK, et al. Fluorinated groups mediate the immunomodulatory effects of volatile anesthetics in acute cell injury. Am J Respir Cell Mol Biol 2011; 45:617–24

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The potential of volatile anesthetics

Cell death programs

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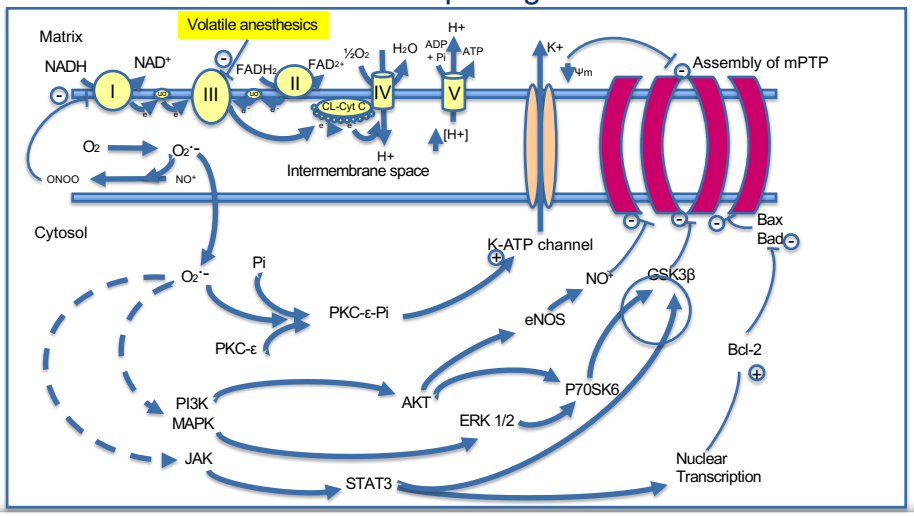
Prevention opening mPTP



Nieuwenhuijs-Moeke G.J. 2018. Adapted from: Andrews DT, Royse C, Royse AG. The mitochondrial permeability transition pore and its role in anaesthesia-triggered cellular protection during ischaemia-reperfusion injury. Anaesth Intensive Care. 2012 Jan;40(1):46-70

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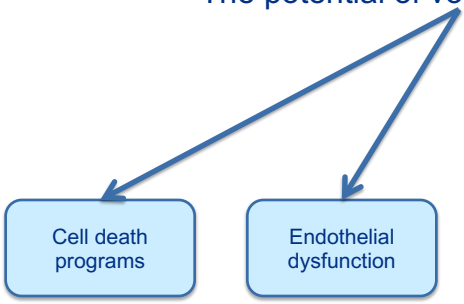

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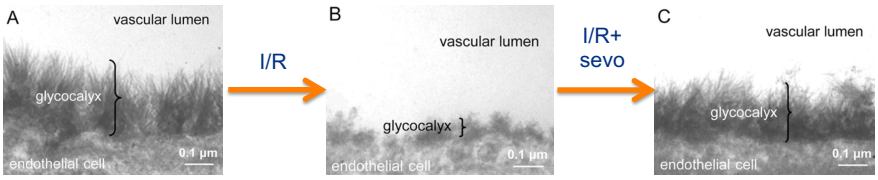
Protection of the glycocalyx

- In vitro and in vivo animal experiments[1,2]
- Pre and post conditioning effective

- ↓ level of extravasation of fluid
- ↓ levels of syndecan-1, heparan sulfate, hyaluronan
- ↓ adhesion of leucocyts/platelets
- Preserved integerity



- Proposed mechanism:↓ release cathespin B

1.Annecke T, Chappell D, Chen C et al. Sevoflurane preserves the endothelial glycocalyx against ischemia-reperfusion injury. Br J Anaesth. 2010; 104(4):414-21
2. Chappell D, Heindl B, Jacob M et al. Sevoflurane reduces leukocyte and platelet adhesion after ischemia-reperfusion by protecting the endothelial glycocalyx Anesthesiology. 2011 Sep;115(3):483-91.

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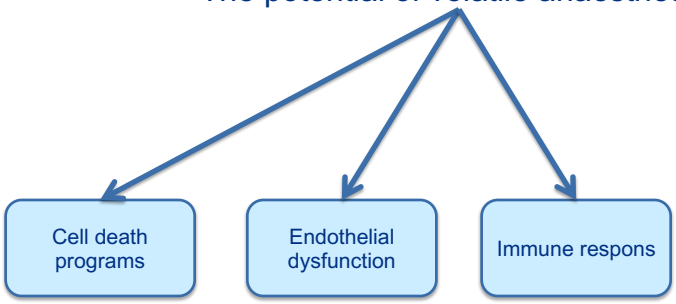

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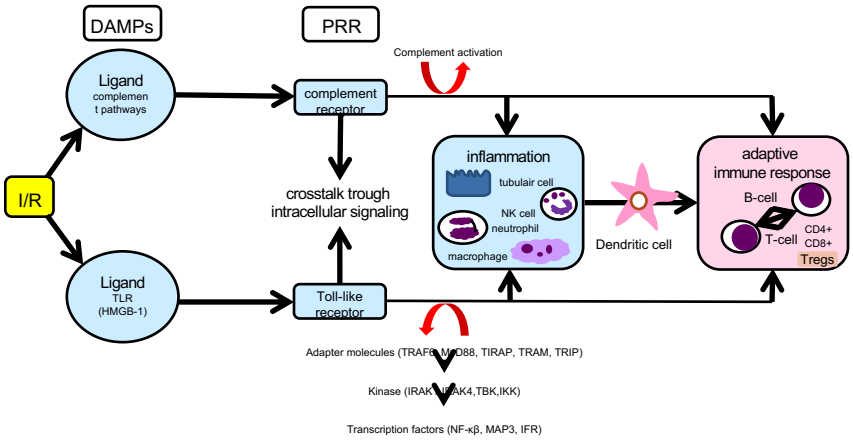
Immune respons in IRI



Nieuwenhuijs-Moeke G.J. Peroperative renal protective strategies in kidney transplantation, PhD thesis, 2018,
Adapted from: Farrar C, Kupiec-Weglinski J, Sacks S. The innate immune sytem and transplantation.
Cold Spring Harb Perspect Med. 2013; 3(10):a015479

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VA and cells of the innate immunesystem

- Neutrophils
  - ↓ cellular function
  - ↓ ROS production
  - ↓ expression of endothelial adhesion molecules and ↓adhesion to endothelium
  - ↓ tissue infiltration
- Monocytes/Macrophages
  - ↓ number
  - ↓ release proinflammatory cytokines IL-1β, TNF-α, IL-6, IL-8
  - ↑ expression iNOS and NO production
  - Influence on APC function unknown
- Natural Killer cells
  - ↓ cytotoxicity
  - ↓ release proinflammatory cytokines
- Dendritic cells
  - Effect unknown

1. Yuki K, Eckenhoff RG. Mechanisms of the Immunological Effects of Volatile Anesthetics: A Review. Anesth Analg. 2016; 123(2):326-35
2. Stollings LM, Jia LJ, Tang P et al. Immune Modulation by Volatile Anesthetics. Anesthesiology. 2016; 125(2):399-411
3. Sedghi S, Kutscher HL, Davidson BA et al. Volatile Anesthetics and Immunity. Immunol Invest. 2017; 46(8):793-804
4.Kurosawa S, Kato M. Anesthetics, immune cells, and immune responses. J Anesth. 2008;22(3):263-77

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VA and cells of the adaptive immune system

- T cells
  - ↓ number and proliferation
  - ↓ Th1/Th2 ratio
  - Induction apoptosis
  - ↓ release proinflammatory cytokines
  - ↓ adhesion molecules
- B cells
  - ↓ number
  - Induction B cell injury
- Tregs
  - Effect unknown

1. Yuki K, Eckenhoff RG. Mechanisms of the Immunological Effects of Volatile Anesthetics: A Review. Anesth Analg. 2016; 123(2):326-35
2. Stollings LM, Jia LJ, Tang P, Dou H, Lu B, Xu Y. Immune Modulation by Volatile Anesthetics. Anesthesiology. 2016; 125(2):399-411
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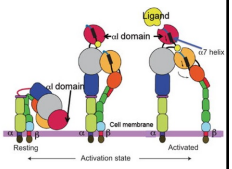
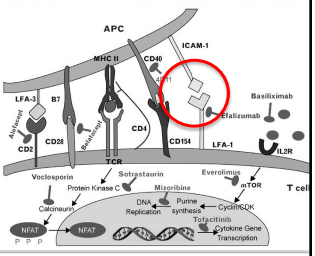
Lymphocyte Function-associated Antigen-I inhibition

- LFA-1, integrin adhesion molecule, expressed on all leukocytes
- Activated by chemokines or antigens
- Ligand: ICAM-1, expression ↑ upon I/R
- LFA-1-ICAM-1 interaction
  - ICAM-1 endothelium: leucocyte transmigration
  - ICAM-1 target cell: activation NK cell, lysis target cell
  - ICAM-1 APC: T cell activation



- Lovastatin binding site, inactive state
- In vitro at clinically relevant concentrations
- Also described for propofol (supranormal concentrations)

- Blockade of LFA-1 is recognized as a potential target to reduces allograft rejection[2]



1. Yuki K, Astrof NS, Bracken C, Soriano SG, Shimaoka M. Sevoflurane binds and allosterically blocks integrin lymphocyte unction-associated antigen-1. Anesthesiology.2010;113:600-9
2. Nicolls MR, Coulombe M, Yang H, Bolwerk A, Gill RG. Anti-LFA-1 therapy induces long-term islet allograft acceptance in the absence of IFN-gamma or IL-4. J Immunol. 2000; 164(7):3627-34

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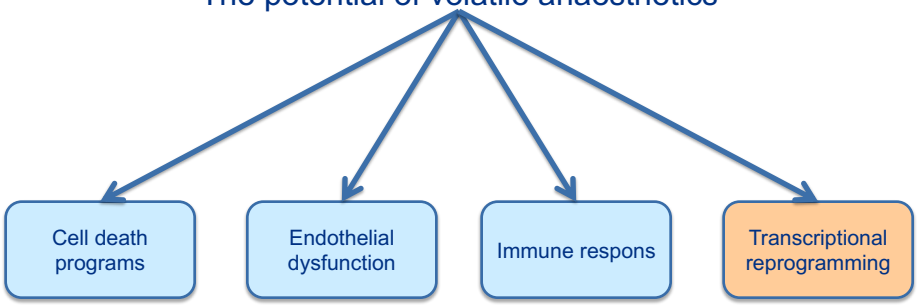
The potential of volatile anaesthetics



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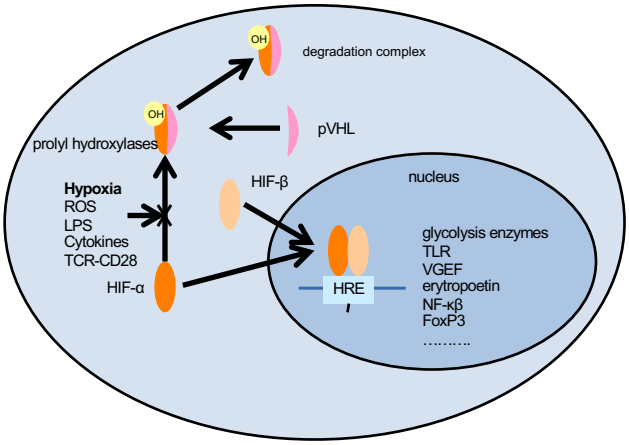
Transcriptional reprogramming



Nieuwenhuijs-Moeke G.J. Peroperative renal protective strategies in kidney transplantation, PhD thesis, 2018

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Upregulation of HIF

- VA are able to upregulate HIF1α,2α
- Possibly via the PI3K/Akt-mTOR pathway

- 15 minutes sevoflurane post conditioning isolated hearts[1]:
  - Upregulation HIF-1α
  - Improved myocardial function
  - Results abolished with 2-methoxyestradiol

- Preconditioning renal I/R model rat[2]:
  - Lower BUN/creatinin levels
  - Higher HIF-2α expression
  - Effect abolished in HIF-2α knock out mice

- Propofol inhibits HIF-1α production

1. Yang L, Xie P, Wu J et al. Sevoflurane postconditioning improves myocardial mitochondrial respiratory function and reduces myocardial ischemia-reperfusion injury by up-regulating HIF-1. Am J Transl Res. 2016; 8(10):4415-24
2. Zheng B, Zhan Q, Chen J et al. Sevoflurane pretreatment enhance HIF-2α expression in mice after renal ischemia/reperfusion injury. Int J Clin Exp Pathol. 2015; 8(10):13114-9

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In conclusion

- VA interfere with many of the processes underlying the pathofysiology of IRI
- Potentially protective effect against IRI
- Effects are dose, timing and context dependant
- Clinical studies are needed

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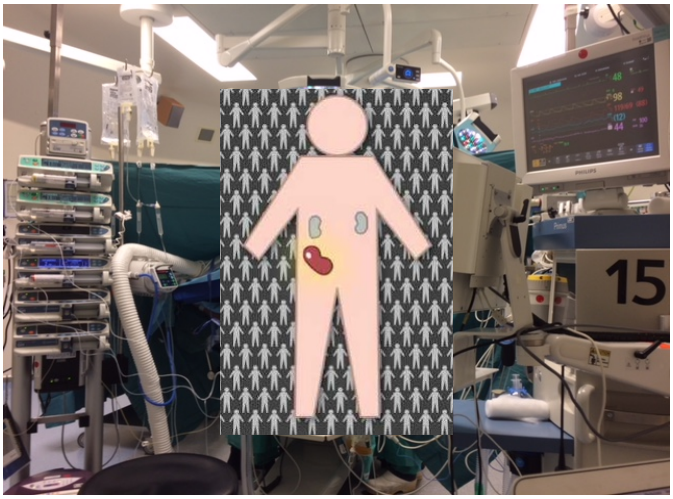

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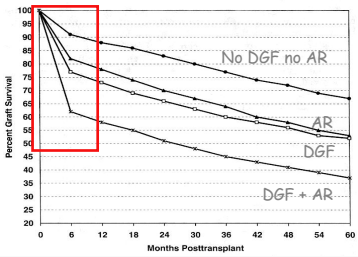
Kidney transplantation

- IRI inevitabel in transplantation
- Consequences of IRI:
  - Delayed graft function (DGF)
  - Primary non function (PNF)
  - Acute rejection (AR)
  - IFTA and Graft loss
  - Influence on short and long term graft outcome
- DGF
  - Increased morbidity,
  - Patients anxiety,
  - Prolonged hospitalization
  - Additional diagnostic procedures and costs



Badet L, Codas R, Barrou B, Hauet T
Department of Kidney and pancreas Transplantation. Lyon France
On behalf of the FLIRT Group Fédération pour l'étude des lésions d'ischémie reperfusion en transplantation

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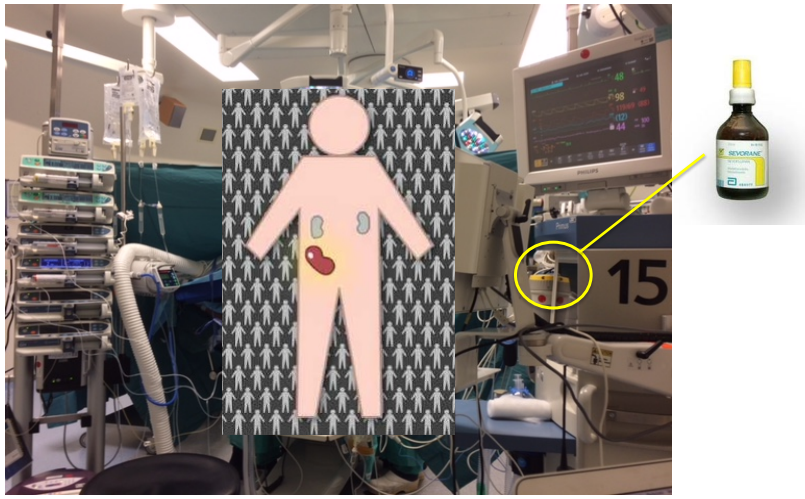

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Anesthetic conditioning kidney

- Rats anesthetised with VA and subjected to renal I/R showed[1]
  - reduced levels of plasma creatinine and cytokines,
  - reduced proinflammatory leucocyte infiltration
  - reduced histological renal necrosis
- Mice, anesthetised with isoflurane and subjected to renal I/R[2]
  - reduction of neutrophil, macrophage and lymphocyte infiltration
- No clinical data

1. Lee HT, Ota-Setlik A, Fu Y et al. Differential protective effects of volatile anesthetics against renal ischemia–reperfusion injury in vivo. Anesthesiology 2004; 101:1313–24
2. Lee HT, Kim M, Kim M, et al. Isoflurane protects against renal ischemia and reperfusion injury and modulates leukocyte infiltration in mice. Am J Physiol Renal Physiol 2007; 293: F713–22

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VAPOR

- **V**(olatile) **A**(naesthetic) **P**(rotection) **O**(f) **R**(enal) transplants trial
- 2-step study
- Difference in renal protective effect of two representative methods of anaesthesia in kidney transplantation.
  - TIVA: propofol-remifentanil based anesthesia
  - Sevoflurane-remifentanil based anesthesia.

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VAPOR-1

- Prospective, single blind, randomized controlled trial
- Living donor kidney transplantation
  - Homogenous model of IRI
  - Reproducible ischemia times
  - Possibility to treat the donor
- Proof of concept
- a sevoflurane based anesthesia is able to induce AC and thereby reduces post-transplant renal injury reflected by a reduced release of kidney injury biomarkers compared to a propofol based anesthesia

Nieuwenhuijs-Moeke GJ, Nieuwenhuijs VB, Seelen MAJ et al. Propofol-based anaesthesia versus sevoflurane-based anaesthesia for living donor kidney transplantation: results of the VAPOR-1 randomized controlled trial. Br J Anaesth. 2017 May 1;118(5):720-732

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VAPOR-1

- Donor and recipient coupled and randomised to one of the three groups:
  - **PROP: PROP**ofol maintenance; 20 couples=40 patients
  - **SEVO: SEVO**flurane maintenance; 20 couples=40 patients
  - **PROSE:** donor **PRO**pofol recipient **SE**voflurane; 20 couples=40 patients
- Primary outcome
  - KIM-1: Kidney injury molecule-1
  - NAG: N-Acetyl-β-D-Glucosaminidase
  - H-FABP: Heart Fatty Acid Binding Protein
- Secondary outcome measures
  - kidney biopsy specimen analysis, serum analysis, mGFR 3, 6 and 12m, DGF, PNF, graft loss, postoperative complications (all kinds), length of hospital stay, Acute rejection
- 2-year follow up

Nieuwenhuijs-Moeke GJ, Nieuwenhuijs VB, Seelen MAJ et al. Propofol-based anaesthesia versus sevoflurane-based anaesthesia for living donor kidney transplantation: results of the VAPOR-1 randomized controlled trial. Br J Anaesth. 2017 May 1;118(5):720-732

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Primary Outcome Measure

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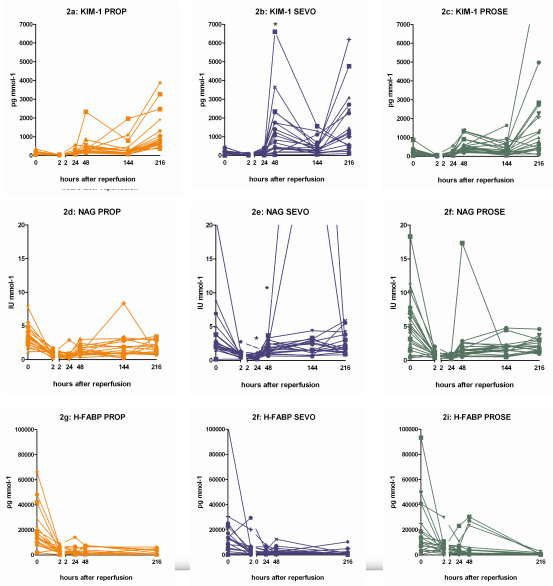
KIM-1

NAG

H-FABP



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Secondary Outcomes Measures

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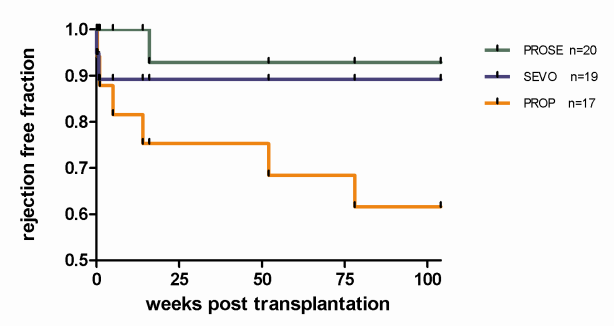
Acute rejection



No ABMR, DSA –

T-cell mediated
- Cellular:
  - PROP 3
  - PROSE 1
- Vascular:
  - PROP 3
  - SEVO 2

Nieuwenhuijs-Moeke GJ, Nieuwenhuijs VB, Seelen MAJ et al. Propofol-based anaesthesia versus sevoflurane-based anaesthesia for living donor kidney transplantation: results of the VAPOR-1 randomized controlled trial. Br J Anaesth. 2017 May 1;118(5):720-732

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In conclusion

- SEVO showed higher urinary KIM-1 and NAG levels in LDKT the 2nd day after transplantation. This was not reflected in inferior graft outcome
- A lower acute rejection rate was seen in the sevo groups.
- Acute rejection = multi-hit model
- An inflammatory environment due to parenchymal injury during transplantation makes the graft more prone to acute and chronic rejection

- Is anesthesia one of the keys to lock the door to rejection?

Nieuwenhuijs-Moeke GJ, Nieuwenhuijs VB, Seelen MAJ et al. Propofol-based anaesthesia versus sevoflurane-based anaesthesia for living donor kidney transplantation: results of the VAPOR-1 randomized controlled trial. Br J Anaesth. 2017 May 1;118(5):720-732

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Next step: VAPOR-2

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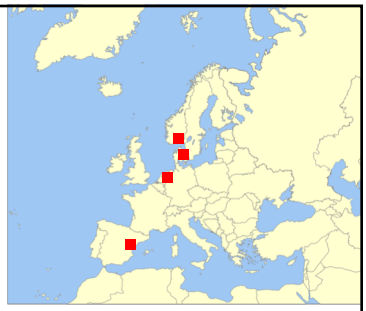
VAPOR-2



- International multicenter RCT
  - University Medical Center Groningen
  - Aarhus university Hospital
  - Fundagio Puigvert Barcelona
  - Oslo University Hospital
- DBD and DCD donors
- 2 groups
  - PROP: PROPofol-remifentanil
  - SEVO: SEVOflurane-remifentanil
- Inclusion started May 2017

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VAPOR-2

- Primary outcome:
  - DGF
  - 488 patients (red in DGF 30%)
- Secondary outcome:
  - graft and patient survival
  - PNF
  - AR
  - biochemical kidney function
  - look in to the mechanisms of protection/immunomodulation with anesthetic agents
    - Immunophenotyping (separate project VAPOR-3)
    - Transcriptomics/proteomics TDI Oxford

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VAPOR-2
anaesthesia matters

www.vapor-2.org

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Thank you

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