



INOX ICU-2:

Insufficient cellular oxygen in ICU patient
with anemia

O₂

Introduction

- Critically ill patients develop anemia (95%¹)
 - 40-50% receive RBC transfusion ^{1,2}
 - Reason transfusion different ¹
- Transfusion trigger 7-8g/dl (4,4-5mmol/l)
 - Probably not all patients have same trigger
- Transfusion possibly associated with ³
 - Mortality
 - LOS↑
 - Organ failure
 - Complications
 - Pulmonary edema
 - 4% transfusion related ¹

1. Corwin HL, Gettinger A, Pearl RG, et al. The CRIT Study: Anemia and blood transfusion in the critically ill—current clinical practice in the United States. *Critical care medicine* 2004;32:39-52.

2. Seitz KP, Sevransky JE, Martin GS, Roback JD, Murphy DJ. Evaluation of RBC Transfusion Practice in Adult ICUs and the Effect of Restrictive Transfusion Protocols on Routine Care. *Critical care medicine* 2016.

3. Hebert PC, Carson JL. Transfusion threshold of 7 g per deciliter—the new normal. *N Engl J Med* 2014;371:1459-61.

Why transfusion?

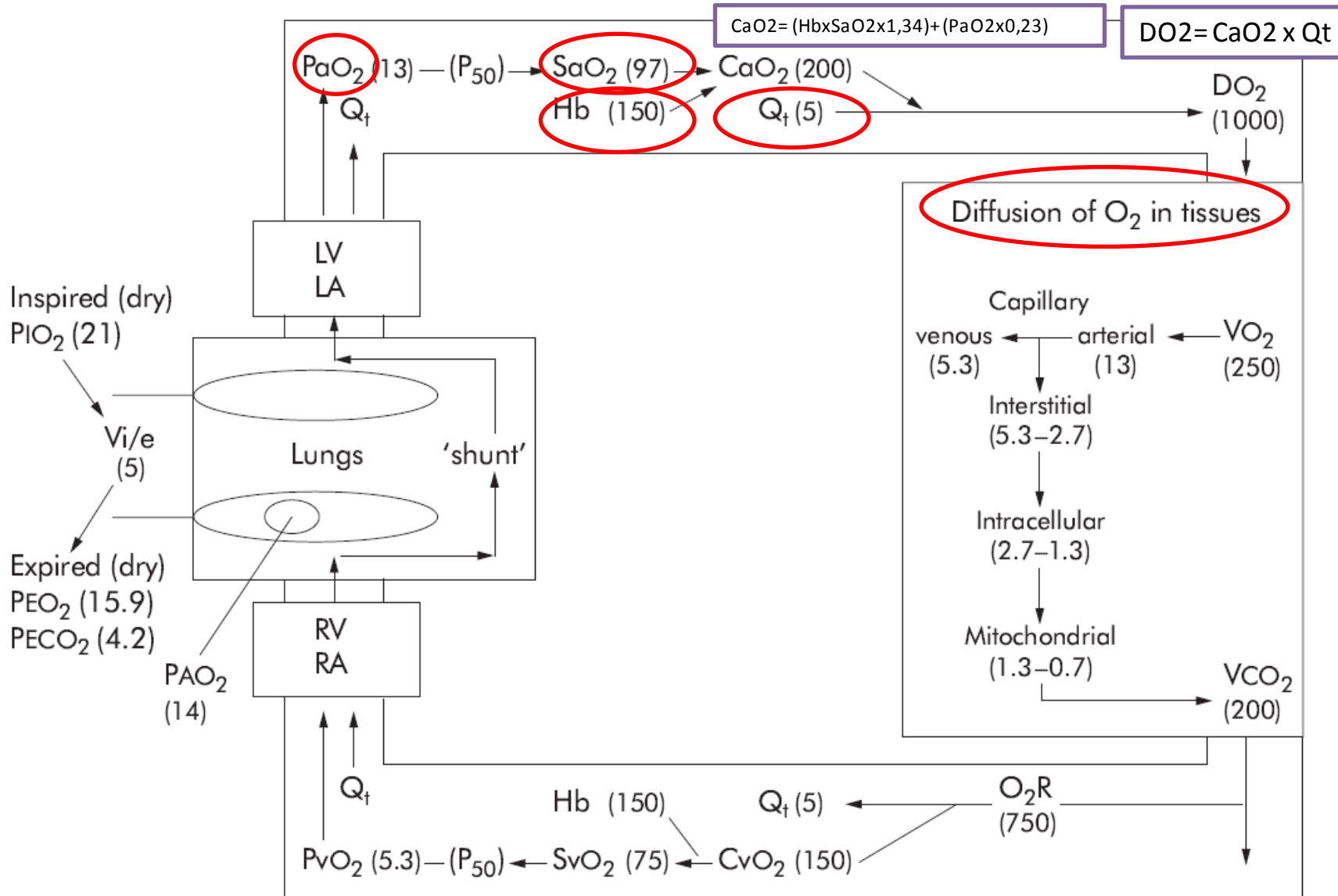
- Oxygen content in arterial blood = $(1.34 \times \text{Hb} \times \text{SaO}_2 \times 0.01) + (0.023 \times \text{PaO}_2)$

Dissolved O₂ in plasma

Hüfner's constant

- Oxygen: 2 unpaired electrons
 - Electrons magnetic
 - Few reactions

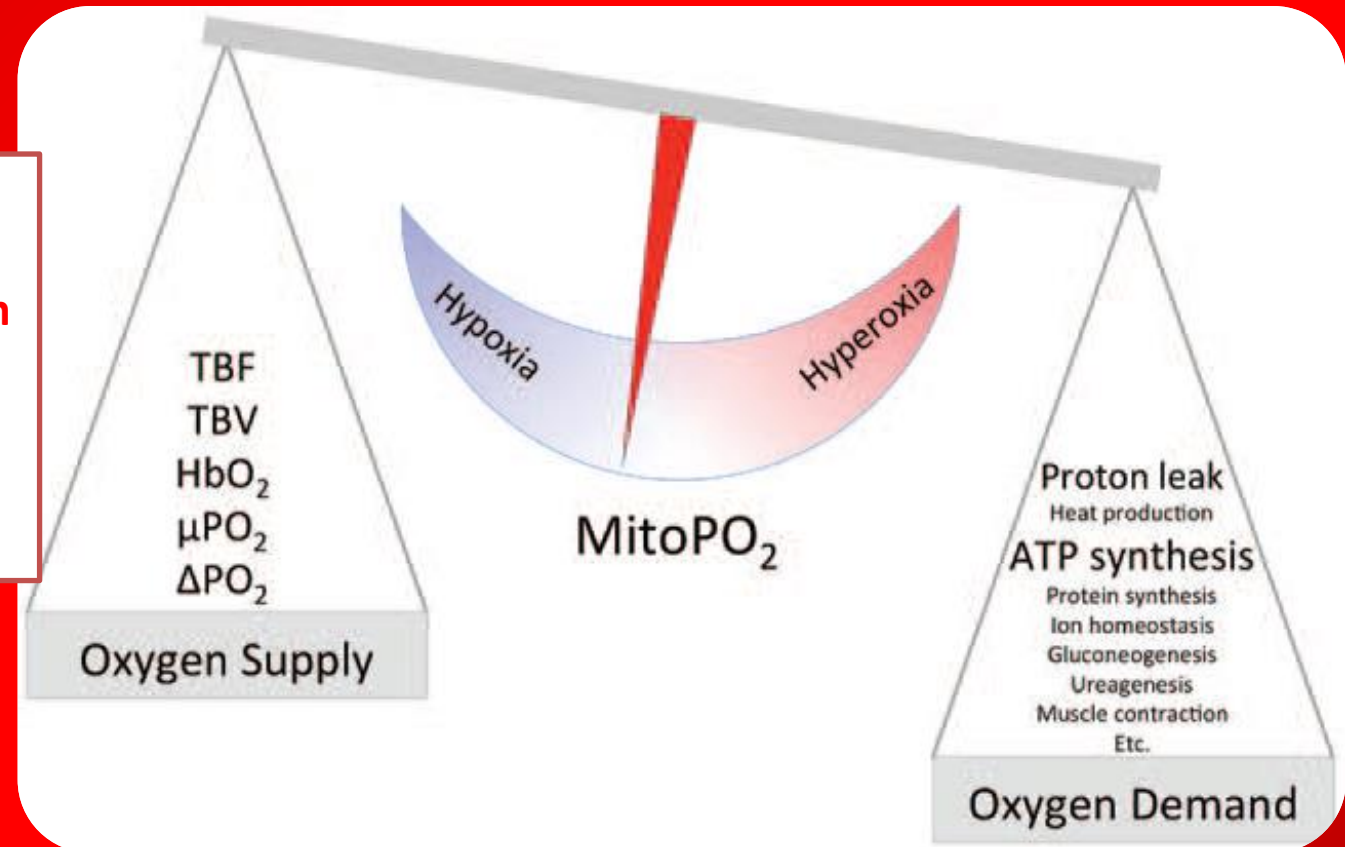
Oxygen transport in healthy individual



$O_2 \rightarrow$ mitochondria \rightarrow oxidative phosphorylation \rightarrow ATP

Effects hypoxia:

- NO production \uparrow
- Anaerobic metabolism \rightarrow lactate \uparrow
- ROS
 - Cell damage
 - Cell death



TBF= tissue blood flow
TBV= tissue blood volume
HbO₂= local hemoglobin saturation
μPO₂= microvascular oxygen tension
ΔPO₂= Oxygen gradient microvessel and mitochondria

Therapeutic targets

- CO
 - Modest predictor mitoPO₂¹
- MAP
 - No ideal target²
- ScvO₂
 - no guarantee of tissue oxygen delivery²
- Lactate
 - Tissue hypoxia, mitochondrial dysfunction, ↓liver clearance¹

- Search for perfusion targets

Protoporphyrin IX-Triplet State Lifetime Technique

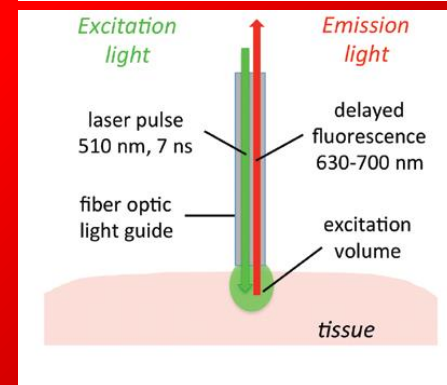
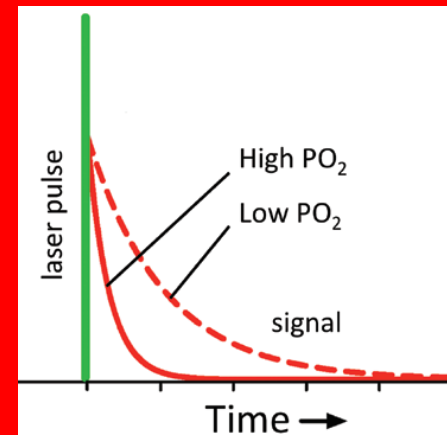
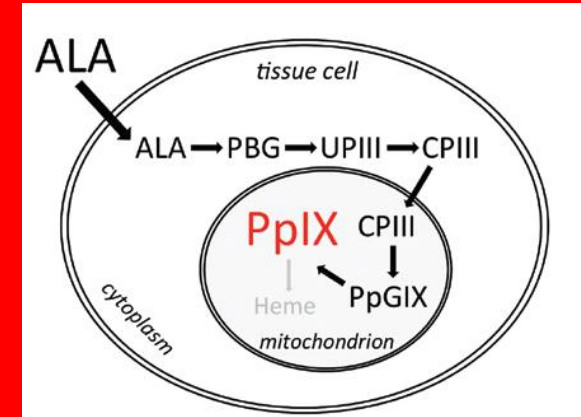


1. Mik EG. Special article: measuring mitochondrial oxygen tension: from basic principles to application in humans. Anesth Analg 2013;117:834-46.

2. Holley A, Lukin W, Paratz J, Hawkins T, Boots R, Lipman J. Review article: Part one: Goal-directed resuscitation – Which goals? Haemodynamic targets. Emergency Medicine Australasia 2012;24:14-22.

Protoporphyrin IX-Triplet State Lifetime Technique-1

- Protoporphyrin IX:
 - Final precursor heme
 - Endogenous synthesized in mitochondria
 - Sensitive
 - Exogenous ALA \rightarrow PpIX \uparrow
 - Photochemical properties
 - Strong reaction with O₂ \rightarrow delayed fluorescence
 - Delayed fluorescence life-time = oxygen tension



Protoporphyrin IX-Triplet State Lifetime Technique-2

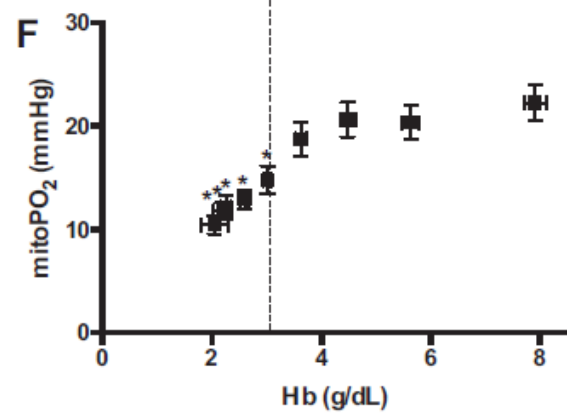
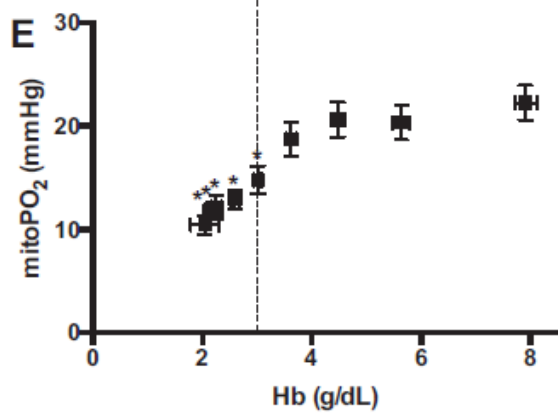
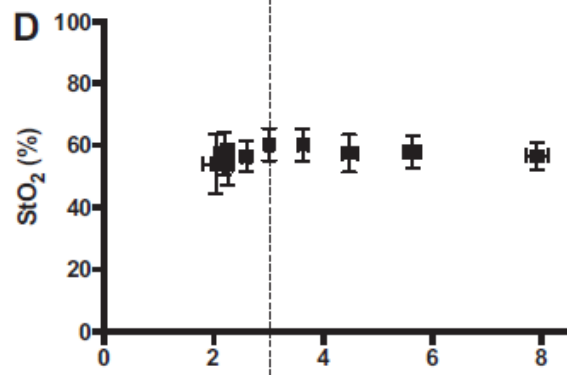
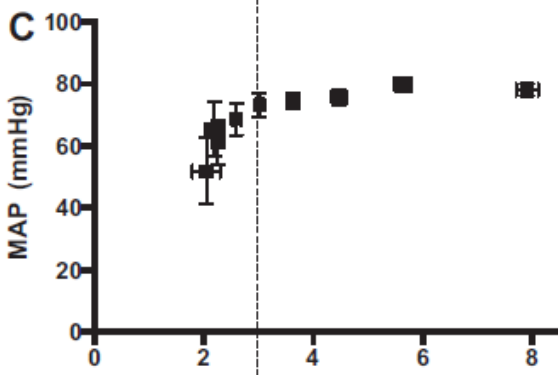
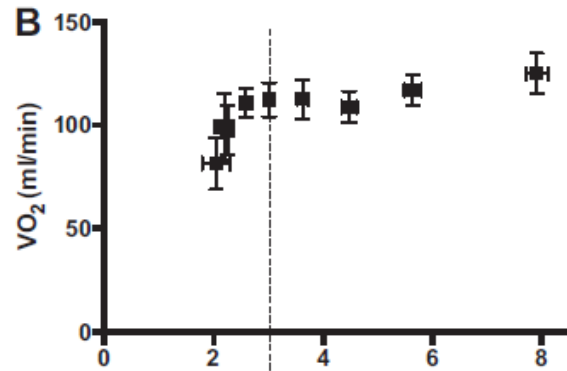
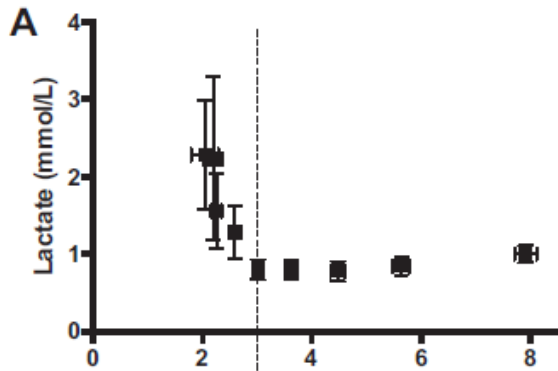
ADVANTAGE

- Noninvasive optical technique
- Quantitative
- No recalibration needed
 - Calibrated & evaluated in different tissues
 - mitoPO2 heterogenous
 - calibration constants constant
- ALA in itself safe

DISADVANTAGE

- ALA needed
- Risk apoptosis in cell via oxygen-radical formation > phototoxicity



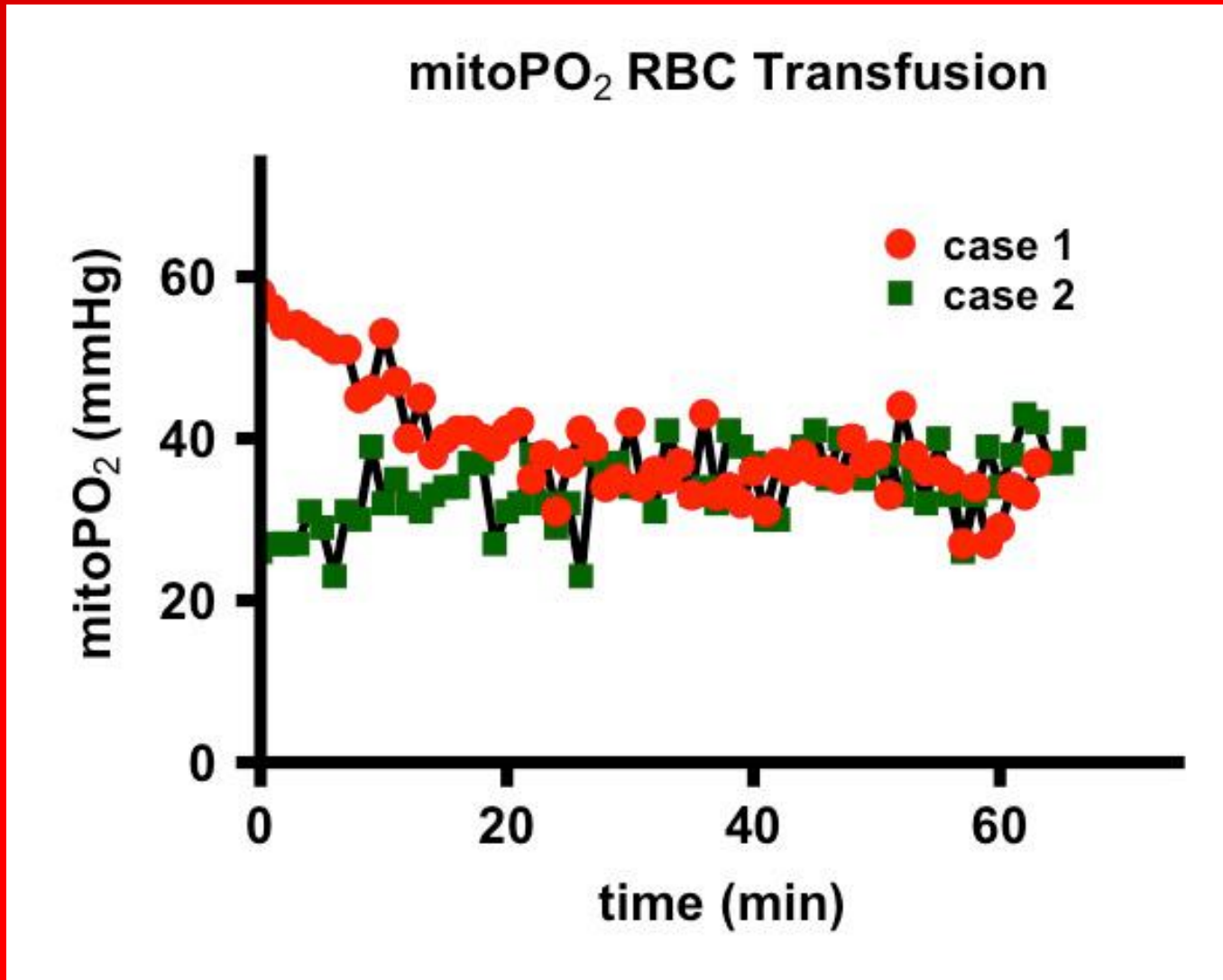


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Fig. Anesthesiology 2016;125:124-32.

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modulation in the

Effect transfusion on mitochondrial oxygenation



Objectives INOX ICU-2

- Feasibility and variability mitoPO2 in ICU patients

Pilot

- Describing effects of red cell transfusion
 - mitoPO2
 - Oxygen balance
 - Tissue oxygenation
- Describing association between mitoPO2 & vital organs

Design & subjects

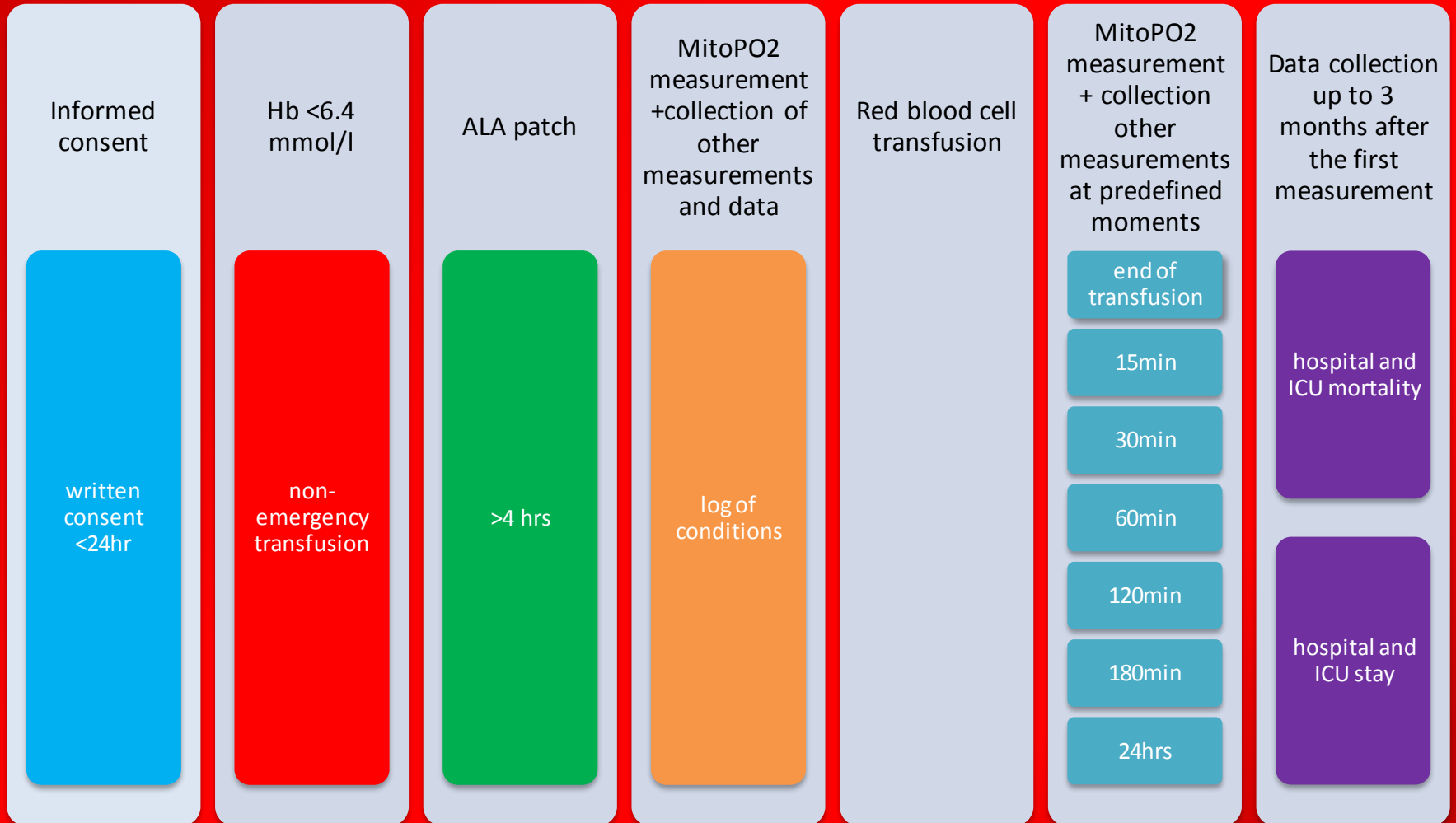
- Design
 - Pilot 20 ICU patients
 - Multicenter prospective cohort study
- Criteria
 - Inclusion: Hb <6.3 mmol/l (<10g/dl) + CVC in situ
 - Exclusion:
 - <18 yrs
 - Emergency red cell transfusion
 - No CVC
 - No informed consent
 - Porphyria and/or known photodermatosis
 - Admission <24hrs on ICU
 - Pregnant or breastfeeding women

Treatment of subjects

- Non-invasive measurement
 - Observational
 - CE marked
- Cutaneous ALA patch
- Skin pad
- Skin sensor
- Phototoxicity



Study procedure



Overview measurements

Standard measurements

- **Daily**
 - creatinin, Hb, lactate, SaO₂, ScvO₂, PvO₂, PaO₂
 - ECG
 - SOFA, RIFLE
- **Continue**
 - SpO₂, HF, BP, CVD, UP, ICDSC, RASS, GCS
 - inotropic therapy, vasopressor use
 - mechanical ventilation duration and setting, renal replacement duration and settings

Extra determinations

- troponin
- CK

Extra measurements

- mitoPO₂ at T0-T7
- ScvO₂, SaO₂, PaO₂, PvO₂ and lactate at T1-6
- Hb measurement at T1
- Cardiac index measurement with Vigilance II at T0 and T7
- Microcirculation with sublingual side stream dark field imaging

Study endpoint

- Main
 - Variability mitoPO₂ with transfusion in critical ill patients
 - Compared with traditional parameters
- Secondary
 - Length of stay
 - Mortality
 - Value of mitoPo₂ in predicting ischemic organ damage
 - Microcirculatory value mitoPO₂
 - Adverse events mitoPO₂ measurements
 - Bias of mitoPO₂ measurements
 - Delay of transfusion

Safety

- Known AE ALA-patch
 - Burning skin, pruritus, hyperpigmentation, erythema, local pain and headache
- Adverse Events and Serious Adverse Events recorded



Risk analysis

- MitoPO2 measurement well investigated
- Quantitative, no recalibration, lifetime measurement
- Technique tested on healthy volunteers
 - Local temporary reaction
 - Risk phototoxicity low
 - Short pulse
 - Low total light dosage
- Study population
 - Minimal risk and burden
 - Clinician stays responsible
 - Max 2 hrs delay transfusion
- Effects mostly local and manageable

Summary

- Feasibility and variability mitoPO₂
- Effect red cell transfusion on mitoPO₂ and other measurements oxygen balance and tissue oxygenation
- Association mitoPO₂ and vital organ functions
- Association mitoPO₂ and microcirculation

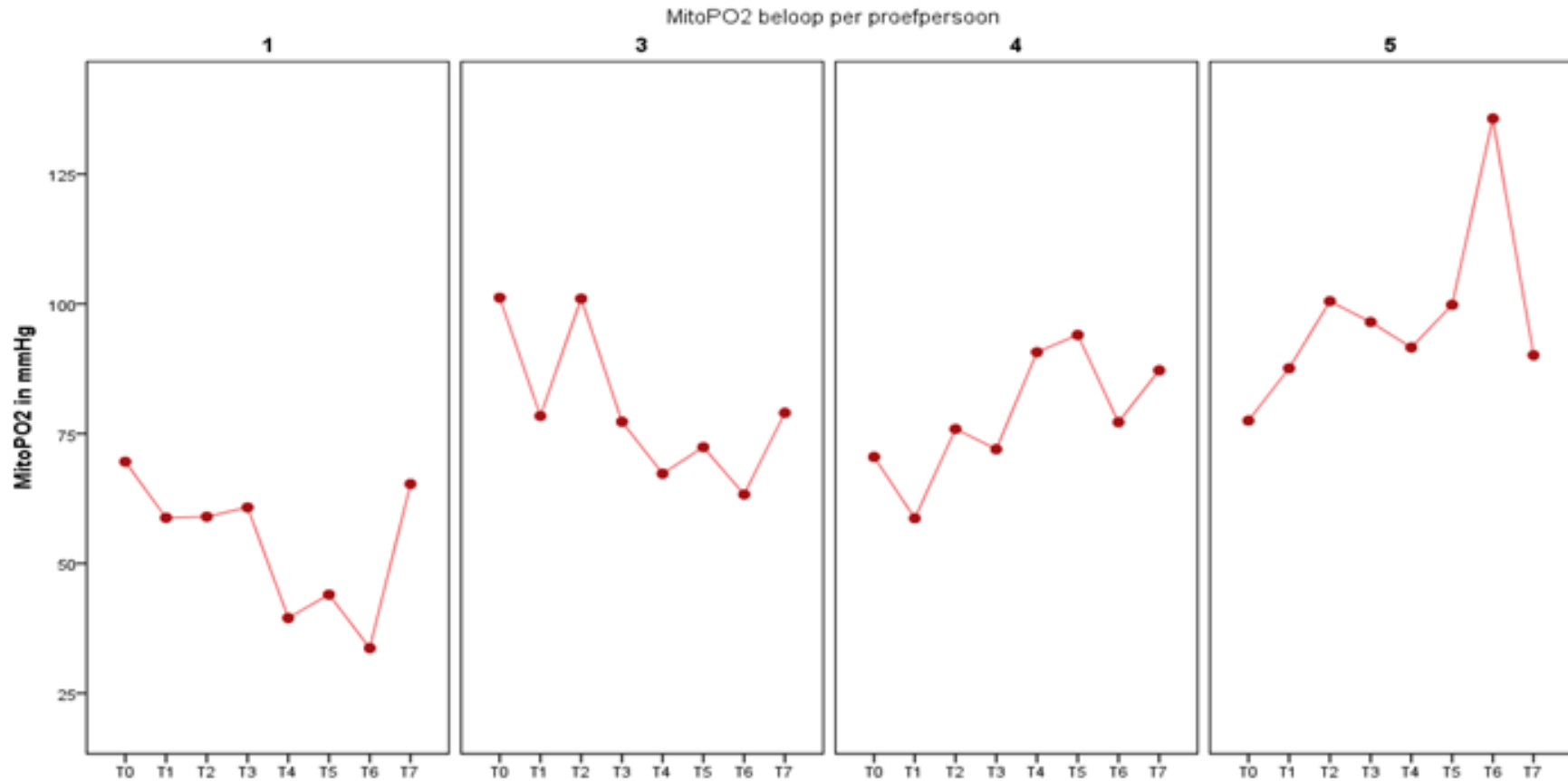
- PpIX-TLST
 - No known serious side-effects
 - Non-invasive
 - Only after informed consent

- Following guidelines of the GCP

Questions?



INOX ICU-2 study





Bloed geven?

Pleister plakken en Meryem bellen

97274

