DO$_2$-guided nephroprotective perfusion -

a non-trivial challenge for a perfusionist

Dirk Buchwald, Krzysztof Klak
Oxygen

- Colorless and odorless gas
- Most common chemical element on earth
- Third most prevalent chemical element in the universe

Highly reactive with most chemical elements of the periodic table

atomic oxygen: $O$
molecular oxygen:
- dioxygen: $O_2$
- trioxygen (ozone): $O_3$
- tetraoxygen: $O_4$
- octaoxygen: $O_8$
Dependence of biological processes on continuous oxygen supply using the example of the human brain

from Siegenthaler, Klinische Pathophysiologie, 2006
- Incidence: over 30 % of all patients

- Independently associated with increased mortality
Oxygen utilization (in normothermia, under resting condition)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>% of CO</th>
<th>$S_{vO_2}$ (%)</th>
<th>% of total-O$_2$-consumption</th>
<th>$Q_{blood}/VO_2$ (ml/min$<em>{blood}$/ml$</em>{O2}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO = 5 l/min</td>
<td>15</td>
<td>69</td>
<td>22</td>
<td>15</td>
</tr>
<tr>
<td>$VO_2^{total.}$ = 225 ml/min</td>
<td>5</td>
<td>37</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>% of total-O$_2$-consumption</td>
<td>22</td>
<td>92</td>
<td>24</td>
<td>73</td>
</tr>
<tr>
<td>$Q_{blood}/VO_2$ (ml/min$<em>{blood}$/ml$</em>{O2}$)</td>
<td>25</td>
<td>66</td>
<td>27</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>17</td>
<td>71</td>
<td>27</td>
<td>14</td>
</tr>
</tbody>
</table>

Why is the kidney so sensitive to hypoxia, although the oxygen extraction rate is so low?
• \( QO_{2\text{kidney}} = 2.7 \text{ mmol/min/kg}, \quad QO_{2\text{heart}} = 4.3 \text{ mmol/min/kg} \)

• This high oxygen consumption is largely driven by the high renal blood flow, since the renal oxygen extraction is low.

• 80 % of the oxygen consumption - tubular sodium transport.

• Basal metabolic rate - 15-20 % of oxygen utilization.
• Renal unique feature:

Increase in RBF → increase in GFR → increase in oxygen demand

• In kidney an increase in oxygen supply also increases the oxygen demand (peculiarity of the kidney)

• Cortex - 20% of CO - tissue $pO_2$ of 20-60 mmHg
  Medulla - 5-10% RBF - tissue $pO_2$ of 10-20 mmHg.

• The segments of the medulla are most vulnerable to the injury caused by low oxygen delivery
Oxygen Delivery During Cardiopulmonary Bypass and Acute Renal Failure After Coronary Operations

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Departments of Cardiothoracic Anesthesia and Intensive Care and Cardiovascular Perfusion, Policlinico San Donato, Milan, Italy

Fig 3. Acute renal failure rate in the study population according to the presence of the two risk factors (low hematocrit and low oxygen delivery).
**Results:** A nadir DO$_2$ level < 262 mL/minute/m$^2$ and a nadir DO$_2$/VCO$_2$ ratio < 5.3 were independently associated with AKI within a model including EuroSCORE and CPB duration. Patients with nadir DO$_2$ levels and nadir DO$_2$/VCO$_2$ ratios below the identified cutoff values during CPB had a significantly higher rate of AKI stage 2 (odds ratios 3.1 and 2.9, respectively). The negative predictive power of both variables exceeded 90%. The most accurate predictor of AKI stage 2 postoperative status was the nadir DO$_2$ level.
Requirements for a nephroprotective perfusion:

Oxygen delivery should be above 262 ml/min/m²

The ratio of oxygen delivery to CO₂ production should be above 5,3
Definition of $\text{DO}_{2i}$: oxygen delivery per square meter of BSA

$$\text{DO}_{2i} = \frac{Q_B \cdot \left( Hb \cdot \frac{S_aO_2}{100} \cdot 1,36 \frac{ml}{g} + 0,0031 \frac{ml}{dl \cdot mm \ Hg \cdot paO_2} \right) \cdot 10 \frac{dl}{l}}{\text{BSA}}$$

where:

- $\text{DO}_{2i}$: oxygen delivery index \( \text{ml/min/m}^2 \)
- $Q_B$: blood flow \( \text{l/min} \)
- $Hb$: hemoglobin \( \text{g/dl} \)
- $S_aO_2$: arterial saturation \( \% \)
- $paO_2$: arterial oxygen partial pressure \( \text{mm Hg} \)
- BSA: body surface area \( \text{m}^2 \)
Control of DO$_{2i}$ during CPB

$$DO_{2i} = Q_B \cdot \left( Hb \cdot \frac{S_aO_2}{100} \cdot 1,36 \frac{ml}{g} + 0,0031 \frac{ml}{dl \cdot mm Hg \cdot paO_2} \right) \cdot 10 \frac{dl}{l}$$

- RAP
- Hemodilution

Perfusion Department
Bochum, Germany
Definition of $VCO_2$: carbon dioxide production

\[ VCO_2 = Q_G \cdot pCO_{2ex} \cdot \frac{1,15}{mmHg} \]

where:

- $VCO_2$ carbon dioxide production (ml/min)
- $Q_G$ oxygenator gas flow (l/min)
- $pCO_{2ex}$ end-tidal carbon dioxide partial pressure (mm Hg)

parameter not directly controllable through the CPB
How can one determine $\text{DO}_2$ and $\text{VCO}_2$ during CPB?
Inline-BGA Monitor

Capnograph

GDP-Monitor

\[ p_{aO_2} \]
\[ S_{aO_2} \]
\[ Hb \]
\[ S_vO_2 \]

\[ pCO_{2exp} \]

\[ DO_2 \]
\[ VCO_2 \]

\[ Q_{blood} \]
\[ Q_{gas} \]
condensed water obstructs gas escape port
recalibration CDI 500

DO₂ rise

DO₂ decline
crystalloid administration

pump flow increase

Packed red blood cells administration

pump stop

low level alarm

Graphik

Datentabelle
How can we verify whether the DO$_2$-guided perfusion has a clinically relevant influence on the renal function?
Definition of the renal failure
Classification of acute renal failure

AKIN (Acute Kidney Injury Network)
RIFLE (Risk Injury Failure Loss Endstage renal disease)

<table>
<thead>
<tr>
<th>RIFLE-Stage</th>
<th>AKIN-Stage</th>
<th>Creatinine criterion</th>
<th>OR</th>
<th>Urine output criterion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk</td>
<td>1</td>
<td>serum creatinine 1,5-2,0 x baseline or increase &gt;0,3 mg/dl</td>
<td>hourly urine output &lt;0,5ml/h/kg for 6-12 h</td>
<td></td>
</tr>
<tr>
<td>Injury</td>
<td>2</td>
<td>serum creatinine 2,0-3,0 x baseline</td>
<td>hourly urine output &lt;0,5 ml/h/kg for &gt; 12 h</td>
<td></td>
</tr>
<tr>
<td>Failure</td>
<td>3</td>
<td>serum creatinine &gt; 3x baseline</td>
<td>hourly urine output &lt; 0,3 ml/h/kg &gt; 24 h or Anuria &gt; 12 h</td>
<td></td>
</tr>
</tbody>
</table>

Disadvantage: Creatinine increases not before GFR falls more than 50%.
Detection of renal failure by means of biological marker

**Cell division cycle**

- IGFBP-7: Insulin-like-growth-factor-binding-protein-7
- TIMP-2: Tissue inhibitor of metalloproteinase-2

Release with damage of tubule cells
C_{IGFBP-7} \times C_{TIMP-2} \quad \text{cut-off value} \quad > 0.3 \text{ ng}^2/\text{ml}^2

- Early detection of ARF in urine
- Shows kidney injury before structural damage occurs (creatinine rise, decrease of GFR)
- Early diagnosis in potentially reversible stage of renal injury
Extended definition of oxygen undersupply
### Definition of cumulative oxygen undersupply \( \text{CU}_{\text{DO}_2} \)

\[
\Delta \text{DO}_2i_t \quad \text{DO}_2i_{\text{actual}} - \text{DO}_2i_{\text{threshold}} \quad \frac{\text{dt}}{\text{m}^2} \\
\Delta \text{DO}_2i = \\text{DO}_2i_{\text{threshold}} - \text{DO}_2i_{\text{actual}} \quad \text{m}^2/\text{min} \\
\]

<table>
<thead>
<tr>
<th>Parameter</th>
<th>pCO2Art_37</th>
<th>pHArt_37</th>
<th>pO2Art_37</th>
<th>TempArt</th>
<th>Ve</th>
<th>DiffOxyAndRedCyt</th>
<th>DO2i/VCO2i</th>
<th>DO2i</th>
<th>VO2i/DO2i</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zeit oberhalb</td>
<td>01:39</td>
<td>01:00</td>
<td>02:00</td>
<td>00:00</td>
<td>00:00</td>
<td>00:40</td>
<td>00:00</td>
<td>01:40</td>
<td></td>
</tr>
<tr>
<td>Obere Grenze</td>
<td>45</td>
<td>7,45</td>
<td>250</td>
<td>37,5</td>
<td>5,00</td>
<td>20,000</td>
<td>500,00</td>
<td>30,00</td>
<td></td>
</tr>
<tr>
<td>Maximum</td>
<td>75</td>
<td>7,49</td>
<td>382</td>
<td>37,4</td>
<td>2,60</td>
<td>190,0935</td>
<td>448,43</td>
<td>36,72</td>
<td></td>
</tr>
<tr>
<td>Durchschnitt</td>
<td>40</td>
<td>7,389207</td>
<td>181</td>
<td>36,6</td>
<td>2,15</td>
<td>7,0461</td>
<td>336,33</td>
<td>22,91</td>
<td></td>
</tr>
<tr>
<td>Minimum</td>
<td>20</td>
<td>7,05</td>
<td>92</td>
<td>24,4</td>
<td>1,80</td>
<td>0,2144</td>
<td>12,48</td>
<td>11,86</td>
<td></td>
</tr>
<tr>
<td>Untere Grenze</td>
<td>35</td>
<td>7,35</td>
<td>150</td>
<td>25,0</td>
<td>1,00</td>
<td>5,3000</td>
<td>272,00</td>
<td>15,00</td>
<td></td>
</tr>
<tr>
<td>Zeit unterhalb</td>
<td>02:00</td>
<td>01:39</td>
<td>10:41</td>
<td>00:00</td>
<td>00:00</td>
<td>18:21</td>
<td>03:19</td>
<td>00:00</td>
<td></td>
</tr>
<tr>
<td>Innerhalb Grenzen</td>
<td>95%</td>
<td>96%</td>
<td>83%</td>
<td>100%</td>
<td>100%</td>
<td>75%</td>
<td>96%</td>
<td>98%</td>
<td></td>
</tr>
</tbody>
</table>
Technical feasibility  Clinical implementation

**Observational study**

- 30 patients
- Continuous recording of \( \text{DO}_2 \) und \( \text{DO}_2 / \text{VCO}_2 \)
- Calculation of the cumulative oxygen undersupply \( (\text{AUC } \text{DO}_2 / t) \)
  - **No change in perfusion management**
- No patient selection
- Measurement of biological marker in urine for early diagnosis of ARF
Results
scheduled: 30 patients  included: 27 patients

3x technical error

n = 27  10 patients developed ARF Stage 1 or 2 within 3 days

ARF according to diuresis- or creatinine criterion

- no ARF
- ARF Stage 1
- ARF Stage 2
Null hypothesis $H_0$: "There is no correlation between postoperative renal failure stage 1 + 2 and urine concentration of biological marker $> 0.3 \text{ng}^2/\text{ml}^2$".

<table>
<thead>
<tr>
<th>Time of analysis</th>
<th>p-value</th>
<th>statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>arrival on ICU</td>
<td>0.9742</td>
<td></td>
</tr>
<tr>
<td>24h postoperative</td>
<td>0.0127</td>
<td>significant</td>
</tr>
</tbody>
</table>

$H_0$ proved wrong:

There is a significant correlation between postoperative renal failure and urine concentration of biological marker.
Cumulative oxygen undersupply $\text{CU}_{\text{DO}_2i}$

Null hypothesis $H_0$: „There is no correlation between the cumulative oxygen undersupply and postoperative renal failure stage 1 + 2.“

<table>
<thead>
<tr>
<th>Oxygen Undersupply $\text{CU}_{\text{DO}_2i}$</th>
<th>p-value</th>
<th>Statistical Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>$&gt; 200 \text{ mlO}_2/\text{m}^2$ and $&lt; 500 \text{ mlO}_2/\text{m}^2$</td>
<td>$0.4559$</td>
<td></td>
</tr>
<tr>
<td>$&gt; 500 \text{ mlO}_2/\text{m}^2$ and $&lt; 1000 \text{ mlO}_2/\text{m}^2$</td>
<td>$0.2388$</td>
<td></td>
</tr>
<tr>
<td>$&gt; 1000 \text{ mlO}_2/\text{m}^2$</td>
<td>$0.0166$</td>
<td>Significant</td>
</tr>
</tbody>
</table>

In patients with cumulative oxygen undersupply $> 1000 \text{ mlO}_2/\text{m}^2$ the occurrence of postoperative renal failure is probable.
Cumulative oxygen undersupply $\text{CU}_{\text{DO}_2i}$

Null hypothesis $H_0$: „There is no correlation between the duration of oxygen undersupply and postoperative renal failure stage 1 + 2 “

<table>
<thead>
<tr>
<th>Duration of oxygen undersupply</th>
<th>p-value</th>
<th>statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>$t &gt; 5 \text{ min and } t &lt; 10 \text{ min}$</td>
<td>0.4093</td>
<td></td>
</tr>
<tr>
<td>$t &gt; 10 \text{ min and } t &lt; 15 \text{ min}$</td>
<td>0.5061</td>
<td></td>
</tr>
<tr>
<td>$t &gt; 15 \text{ min}$</td>
<td>0.0236</td>
<td>significant</td>
</tr>
</tbody>
</table>

In patients with duration of undersupply of $\text{DO}_2i > 15 \text{ min}$ the occurrence of postoperative renal failure is probable.
Duration of ECC

Null hypothesis $H_0$:
„There is no correlation between the bypass time and postoperative renal failure stage 1 + 2“

<table>
<thead>
<tr>
<th>CPB duration</th>
<th>p-value</th>
<th>statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 100 min</td>
<td>0,2467</td>
<td></td>
</tr>
<tr>
<td>&gt; 100 min and &lt; 120 min</td>
<td>0,6559</td>
<td></td>
</tr>
<tr>
<td>&gt; 120 min and &lt; 140 min</td>
<td>0,4559</td>
<td></td>
</tr>
</tbody>
</table>

In considered time frame until 140 minutes of CPB time the null hypothesis was confirmed.
Conclusions

• During low-flow phases of the CPB and/or too low hemoglobin level \( \text{DO}_2 \text{i} \) can fall below the critical value of 272 \( \text{ml/min/m}^2 \) for longer time periods, although the venous saturation (gold standard) is high enough.

• \( \text{DO}_2 \text{i} \) below critical level (also for short time periods) -> cumulative pathological effect for renal function

• The biological markers IGFBP-7 and TIMP-2 sensitively detect renal failure.

• The implementation of \( \text{DO}_2 \)-guided perfusion as „Goal Directed Perfusion (GDP)“

is for perfusionists technically (and intellectually) practicable,

requires however „extended perception“ compared to the daily CPB routine.
Coming soon:

**G.I.F.T. Trial**
Goal Directed Perfusion Trial

Multicenter study (11 centers, 40-80 patients per center, max. 700 patients)

PI Ranucci, Milano

<table>
<thead>
<tr>
<th>CONTROL (N=350)</th>
<th>TREATMENT (N=350)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GDP monitor</td>
<td>GDP monitor</td>
</tr>
<tr>
<td>No blood prime (withdrawal)</td>
<td>No blood prime (withdrawal)</td>
</tr>
<tr>
<td>Priming volume and nature according to local standards</td>
<td>Priming volume and nature according to local standards</td>
</tr>
<tr>
<td>Perfusion targeted on BSA and °C</td>
<td><strong>Perfusion targeted on DO\textsubscript{2} \geq 280 \text{ ml/min/m}\textsuperscript{2}</strong></td>
</tr>
<tr>
<td>Perfusion pressure according to local standards</td>
<td>Perfusion pressure according to local standards</td>
</tr>
<tr>
<td><strong>Transfusion triggered by Hct according to local standards</strong></td>
<td><strong>Transfusion triggered by S\textsubscript{a}O\textsubscript{2} &lt; 68% and/or O\textsubscript{2}ER &gt; 40%</strong></td>
</tr>
<tr>
<td>Postoperative care according to local standards</td>
<td>Postoperative care according to local standards</td>
</tr>
</tbody>
</table>
Disclosure

Speaker’s fee, travel expenditures, hotel room from Sorin Group

Thank you for your attention.