Transmission of arterial oxygen partial pressure oscillations to the cerebral microcirculation in a porcine model of acute lung injury caused by cyclic recruitment and derecruitment

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Editor’s key points
- Cyclic recruitment and derecruitment of lung units lead to oscillations in arterial oxygen partial pressure and are involved in the pathophysiology of acute lung injury.
- In this experimental study in a pig model, oscillations were also observed in cerebral oxygen partial pressure and blood flow.
- Oscillations in cerebral and systemic oxygenation might contribute to the interaction between acute lung and brain injury.

Background. Cyclic recruitment and derecruitment (R/D) play a key role in the pathomechanism of acute lung injury (ALI) leading to respiration-dependent oscillations of arterial partial pressure of oxygen (\(P_{aO_2}\)). These \(P_{aO_2}\) oscillations could also be forwarded to the cerebral microcirculation.

Methods. In 12 pigs, partial pressure of oxygen was measured in the thoracic aorta (\(P_{aO_2}\)) and subcortical cerebral tissue (\(P_{brO_2}\)). Cerebral cortical haemoglobin oxygen saturation (\(S_{brO_2}\)), cerebral blood flow (CBF), and peripheral haemoglobin saturation (\(S_{pO_2}\)) were assessed by spectroscopy and laser Doppler flowmetry. Measurements at different fractions of inspired oxygen (\(FIO_2\)) were performed at baseline and during cyclic R/D. Statistics: frequency domain analysis, the Mann–Whitney test, linear models to test the influence of \(P_{aO_2}\) and systolic arterial pressure (SAP) oscillations on cerebral measurements.

Results. Parameters [mean (SD)] remained stable during baseline. \(P_{aO_2}\) oscillations [10.6 (8) kPa, phase reference], systemic arterial pressure (SAP) oscillations [20 (9) mm Hg, phase \(P_{aO_2} - SAP = 33 (72)\)] , and \(S_{pO_2}\) oscillations [1.9 (1.7)%, phase \(P_{sO_2} - S_{pO_2} = 264 (72)\)] were detected during lung R/D at \(FIO_2\) 1.0. \(P_{aO_2}\) oscillations decreased [2.7 (3.5) kPa, \(P=0.0008\)] and \(S_{pO_2}\) oscillations increased [6.8 (3.9)%, \(P=0.0014\)] at \(FIO_2\) 0.3. In the brain, synchronized \(P_{brO_2}\) oscillations [0.6 (0.4) kPa, phase \(P_{brO_2} - P_{brO_2} = 90 (39)\) ], \(S_{brO_2}\) oscillations [4.1 (1.5)%, phase \(P_{brO_2} - S_{brO_2} = 182 (54)\) ], and CBF oscillations [198 (176) AU, phase \(P_{CBF} = 201 (63)\) ] occurred that were dependent on \(P_{aO_2}\) and SAP oscillations.

Conclusions. \(P_{aO_2}\) oscillations caused by cyclic R/D are transmitted to the cerebral microcirculation in a porcine model of ALI. These cyclic oxygen alterations could play a role in the crosstalk of acute lung and brain injury.

Keywords: brain, blood flow; brain, oxygen consumption; lung, respiratory distress syndrome; measurement techniques, oximeters; oxygen, partial pressure

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Mechanical ventilation is critical for the survival of patients with acute lung injury (ALI) or acute respiratory distress syndrome (ARDS). A protective ventilator strategy using low tidal volumes (\(V_T\)) and limited inspiratory plateau pressure (\(P_{Plat}\)) has been associated with a reduction in mortality.1 This approach, however, may result in increased recruitment and derecruitment (R/D) and aggravate ventilator-induced lung injury (VILI).2 It has been demonstrated that varying pulmonary shunt fraction attributed to R/D within the respiratory cycle (cyclic R/D) leads to aortic \(P_{aO_2}\) oscillations. This mechanism has been described at high temporal resolution using novel fast oxygen-sensing technology.3 4

The impact of cyclic R/D and consequent \(P_{aO_2}\) oscillations on vital organs such as the heart, kidney, and brain is unknown. Alterations in oxygen supply to the brain could affect neuronal tissue integrity. This hypothesis is consistent with the observation that the majority of patients with ALI/ARDS develop neuronal dysfunction associated with morphological brain damage.5 6 Furthermore, evidence from sleep apnoea research suggests that cyclic alterations in oxygenation can promote neuronal dysfunction.7 8 9 However, the influence of cyclic R/D-associated \(P_{aO_2}\) oscillations on cerebral microcirculation has not been investigated.

In the present study, we investigated the following hypotheses: (i) cyclic R/D induces respiratory-dependent oscillations of the following parameters: arterial partial pressure of oxygen (\(P_{aO_2}\)), peripheral haemoglobin oxygen saturation (\(S_{pO_2}\)), cerebral subcortical partial pressure of oxygen
(PbrO$_2$), cerebral cortical haemoglobin oxygen saturation (SbrO$_2$), and cerebral cortical blood flow (CBF) at the capillary-venous level; (ii) altered fractions of inspired oxygen affect the amplitude of these oscillations; and (iii) variations in systolic arterial pressure (SAP) influence cerebral oscillations.

**Methods**

After approval by the governmental animal care committee (Rhineland-Palatinate, Germany, approval number G09-1-037), 12 juvenile pigs (German country race, weight 25–27 kg) were investigated. These studies conformed to ARRIVE guidelines.

**Anaesthesia and preparation**

After i.m. sedation (ketamine 8 mg kg$^{-1}$ and midazolam 0.2 mg kg$^{-1}$) and vascular access via ear vein, anaesthesia was induced i.v. (fentanyl 4 μg kg$^{-1}$, propofol 4 mg kg$^{-1}$, atracurium 0.5 mg kg$^{-1}$) to facilitate tracheal intubation (tube inner diameter 8.0 mm). Anaesthesia was maintained by continuous infusion (fentanyl 0.1–0.4 mg kg$^{-1}$ h$^{-1}$ and propofol 8–12 mg kg$^{-1}$ h$^{-1}$). A standard pressure-controlled ventilatory regimen was initiated with a tidal volume (VT) of 10–12 ml kg$^{-1}$, PEEP of 5 cm H$_2$O, FIO$_2$ of 0.3–0.4, inspiration to expiration ratio (I:E) of 1:2, and variable respiratory rate (RR) to maintain normocapnia (Servo 900 C, Siemens, Erlangen, Germany). Sterofundin solution (Braun, Melsungen, Germany) was infused continuously (5 ml kg$^{-1}$ h$^{-1}$). The following vascular catheters were placed by surgical cut-down: an arterial line and a PICCO catheter (Pulsion Medical Systems, Munich, Germany) via the right femoral artery; a central venous line via the right femoral vein; an arterial introducer for fast measurements for PO$_2$ via the left femoral artery. Haemodynamic and spirometric measurements were sampled at 100 Hz using Philips S5 monitoring software (S5 Collect, Datex Ohmeda GmbH, Duisburg, Germany). Fast haemoglobin oxygen saturation (S$_{O2}$) measurement was performed at the pig tail.

A craniotomy (20×10 mm) was performed 5 mm from the midline and 5 mm behind the coronal suture for positioning of the cerebral subcortical PO$_2$ probe (PbrO$_2$) and the combined cerebral cortical haemoglobin oxygen saturation (SbrO$_2$) and CBF monitoring probe. Because the dura was opened for positioning of the probes, intracerebral pressure was not measured. The head was wrapped in plastic foil to fixate the experimental setting. The time to prepare the experiments took about 4–6 h including craniotomy and positioning of probes. Postmortem the brain was removed, correct positioning of the probes was verified, and the surrounding tissue was examined for cerebral haemorrhage. A Rapidlab 248 device (Bayer Healthcare, Leverkusen, Germany) was used for arterial blood gas analysis (BGA). Temperature was measured by a pericranial temperature probe (Temp) placed in the temporal muscle. Body surface warming was performed by a heating blanket system. Cardiac index was assessed by single-indicator transpulmonary thermodilution using the PICCO system.

**10 Hz fluorescence quenching of oxygen (Foxy AL-300)**

Simultaneous measurements of PO$_2$ in the thoracic aorta and PbrO$_2$ 14 mm deep from brain surface were performed using uncoated 10 Hz fluorescence quenching of oxygen technology (Foxy-AL300, Ocean Optics, Dunedin, FL, USA).

These PO$_2$ probes are fiberoptic, aluminium-jacketed probes with an uncoated ruthenium complex at the probe tip allowing for ultrafast measurements at 10 Hz. The probes were calibrated in vitro according to the manufacturer’s instruction. The validity of the calibration was confirmed by conventional BGA.

**2.5 Hz white light photo-spectrometry and 20 Hz laser-Doppler flowmetry (O2C-device)**

SbrO$_2$ (%) and CBF (AU) of the cerebral cortex at the capillary venous level were measured by combined 2.5 Hz white light spectroscopy and 20 Hz laser Doppler flowmetry (O$_2$C-Device, LEA Medizintechnik GmbH, Giessen, Germany). Returning light is split into its spectral components by a charge-coupled device array and multiple white light wavelengths are detected simultaneously (500–630 nm, <30 mW). The spectrum is compared with universal reference values of deoxygenated and oxygenated haemoglobin spectra to determine SbrO$_2$. A Doppler shift of the illuminated laser light (830 nm, <30 mW) caused by movements of erythrocytes is detected and analysed as CBF.

**1.0 Hz multi-wavelength spectrometry (Masimo SET)**

The Masimo SET-R-Device (Masimo SET-R, Masimo, Irvine, FL, USA) uses a new-generation multi-wavelength sensor. A special research version was provided by the manufacturer allowing for continuous non-invasive peripheral haemoglobin saturation (S$_{O2}$) measurements at 1.0 Hz.

**Experimental protocol**

Ventilator settings were adjusted for baseline conditions defined as VT 10–12 ml, PEEP 5 cm H$_2$O, P$_{peak}$ <30 cm H$_2$O, I:E 1:2, and RR 25–30 to maintain normocapnia (4.6–6 kPa PaCO$_2$). Measurements were performed at FIO$_2$ 1.0 (baseline 1.0) and 0.3 (baseline 0.3) in a random fashion. During each measurement period, 1800–2400 single PO$_2$ and PbrO$_2$ measurements, 450–600 single SbrO$_2$ measurements, 3600–4800 single CBF measurements, and 180–240 single S$_{O2}$ measurements were recorded.

ALI was induced by repetitive bronchoalveolar lavage. The tracheal tube was clamped in inspiration and 30 ml kg$^{-1}$ of warmed Sterofundin solution (Braun) was instilled by gravity and afterwards immediately removed. This procedure was repeated until the PAO$_2$/FI O$_2$ ratio was <300 at a PEEP of 5 cm H$_2$O for >60 min. Ventilator settings were adjusted as follows: VT >20 ml kg$^{-1}$, PEEP 0 cm H$_2$O (ZEEP), P$_{peak}$ >30 cm H$_2$O, I:E 1:4, and RR 5 to provoke cyclic R/D and consecutive PO$_2$ oscillations. Measurements during cyclic R/D were repeated at FI O$_2$ 1.0 (cyclic R/D 1.0) and 0.3 (cyclic R/D 0.3) in a random fashion. The experimental protocol including
induction of ALI and measurements at baseline conditions and cyclic R/D lasted about 4–6 h.

**Statistical methods**

Data are presented as mean (so). Comparisons were performed using the Mann–Whitney test. P-values below 0.05 were considered significant. Frequency domain analysis was performed using Mathcad (Mathcad 2000, Mathsoft, Cambridge, MA, USA) and Igor Pro (Igor Pro 6.22a, WaveMetrics, Lake Oswego, OR, USA) for the calculation of waveform amplitudes, frequencies, phase shift as referred to $P_{aO_2}$ oscillations (phase reference), and Fourier spectra. Linear models using the Bonferroni correction were fitted to test the influence of spectra. Linear models using the Mann–Whitney test.

**Results**

The experimental set-up was successful in all animals. The applied respiratory mechanics, haemodynamic variables, and blood gas analyses are summarized in Table 1.

**Baseline conditions**

During baseline, measurements of systemic ($P_{aO_2}$), peripheral ($S_{PO_2}$), and cerebral ($P_{brO_2}$, $S_{brO_2}$) oxygenation remained constant as indicated by small amplitudes ($\Delta$) (Table 2). Likewise, physiological SAP variation and CBF oscillations remained within normal limits (Table 2). All measured variables remained stable over time and were not influenced by the RR as illustrated in representative Figure 1.

**Cyclic R/D**

After induction of ALI [lavage 2 (3) times] and during cyclic R/D at $FIO_2$ 1.0, respiratory-dependent oscillations in systemic oxygenation [mean $P_{aO_2}$ oscillations 10.6 (8) kPa, $P_{brO_2}$, $S_{brO_2}$], and circulation [mean $S_{brO_2}$ oscillations 1.9 (1.7)%, phase $P_{brO_2}$–$S_{brO_2}$ 264 (72)°] was observed (Table 2). These oscillations were related to an RR of 5 bpm as confirmed by the Fourier transformation (peak at 0.08333 Hz $\times$ 60 = 4.999, $P<0.05$).

Synchronized respiratory-dependent oscillations were detected in subcortical [mean $P_{brO_2}$ oscillations 0.6 (0.4) kPa, phase $P_{brO_2}$–$P_{brO_2}$ 90 (39)°] and cortical [mean $S_{brO_2}$ oscillations 4.1 (1.5)%, phase $P_{brO_2}$–$S_{brO_2}$ 182 (54)°] brain tissue as illustrated in representative Figure 2 (Table 2, $P<0.05$). At $FIO_2$ 0.3, the mean $P_{aO_2}$ oscillations decreased to 2.7 (3.5) kPa ($P=0.0008$, Fig. 3) and SAP oscillations remained unchanged ($P=0.6235$). Contrariwise, the mean $S_{brO_2}$ oscillations increased from 1.9 (1.7)% to 6.8 (3.9)% and the mean $S_{brO_2}$ oscillations tended to increase from 4.1 (1.5)% to 8.5 (6.6)% at $FIO_2$ 0.3 ($P=0.0524$, Fig. 3). The phase shifts between

### Table 1: Haemodynamics, respiratory mechanics, and gas exchange during baseline and cyclic recruitment and derecruitment (cyclic R/D) at $FIO_2$ 1.0 and 0.3. Data are presented as mean (so). Comparisons between baseline and cyclic R/D were performed by the Mann–Whitney test. CI, cardiac index; cyclic R/D, recruitment and derecruitment; ELWI, extravascular lung water index; $FIO_2$, fraction of inspired oxygen; $Hb$, haemoglobin; HR, heart rate; $I/E$, inspiratory to expiratory ratio; MAP, mean arterial pressure; NS, non-significant; $P_{aco_2}$, arterial carbon dioxide partial pressure; $P_{apeak}$, arterial oxygen partial pressure; $P_{aPaco_2}$, plateau airway pressure; PEEP, positive end-expiratory pressure; RR, respiratory rate; $S_{PO_2}$, peripheral haemoglobin saturation; Temp, pericranial temperature; $V_{E}$, minute ventilation; $V_T$, tidal volume.

<table>
<thead>
<tr>
<th>$FIO_2$</th>
<th>Baseline</th>
<th>Cyclic R/D</th>
<th>$P$-value</th>
<th>$FIO_2$</th>
<th>Baseline</th>
<th>Cyclic R/D</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mm Hg)</td>
<td>89 (20)</td>
<td>73 (8)</td>
<td>NS</td>
<td>90 (17)</td>
<td>71 (14)</td>
<td>0.0181</td>
<td></td>
</tr>
<tr>
<td>HR (beats min$^{-1}$)</td>
<td>98 (14)</td>
<td>125 (34)</td>
<td>0.0262</td>
<td>106 (16)</td>
<td>155 (26)</td>
<td>0.0004</td>
<td></td>
</tr>
<tr>
<td>CI (litre min$^{-1}$ m$^{-2}$)</td>
<td>4.0 (1.0)</td>
<td>4.6 (1.3)</td>
<td>NS</td>
<td>4.2 (0.9)</td>
<td>4.5 (1.3)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Temp ($^\circ$C)</td>
<td>37.0 (1.4)</td>
<td>37.7 (1.2)</td>
<td>NS</td>
<td>37.2 (1.3)</td>
<td>37.0 (1.3)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>RR (bpm)</td>
<td>28 (4)</td>
<td>4.9 (0.1)</td>
<td>&lt;0.0001</td>
<td>29 (5)</td>
<td>5.0 (0)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>$V_T$ (ml)</td>
<td>330 (46)</td>
<td>1070 (217)</td>
<td>&lt;0.0001</td>
<td>320 (55)</td>
<td>997 (260)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>$V_{E}$ (litre min$^{-1}$)</td>
<td>8.9 (1.7)</td>
<td>5.0 (1.0)</td>
<td>&lt;0.0001</td>
<td>9.6 (1.7)</td>
<td>4.7 (1.2)</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>$P_{apeak}$ (cm H$_2$O)</td>
<td>20.6 (5.3)</td>
<td>46.8 (7.4)</td>
<td>&lt;0.0001</td>
<td>21.3 (4.8)</td>
<td>47.7 (8)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>$P_{aPaco_2}$ (cm H$_2$O)</td>
<td>18.4 (4.1)</td>
<td>43.8 (8.2)</td>
<td>&lt;0.0001</td>
<td>18.4 (4.1)</td>
<td>44.9 (8.2)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>PEEP (cm H$_2$O)</td>
<td>4.7 (0.8)</td>
<td>0 (0.1)</td>
<td>&lt;0.0001</td>
<td>4.6 (1.3)</td>
<td>0.6 (0.3)</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>ELWI (ml kg$^{-1}$)</td>
<td>14.2 (3.3)</td>
<td>22.9 (10)</td>
<td>0.0026</td>
<td>14.5 (3)</td>
<td>22.9 (10)</td>
<td>0.0057</td>
<td></td>
</tr>
<tr>
<td>$I/E$ (ratio)</td>
<td>1.20 (0.6)</td>
<td>1.34 (0.9)</td>
<td>0.0009</td>
<td>1.21 (0.7)</td>
<td>1.37 (1.1)</td>
<td>0.0014</td>
<td></td>
</tr>
<tr>
<td>$P_{aco_2}$ (kPa)</td>
<td>5.5 (0.7)</td>
<td>7.8 (2)</td>
<td>0.0043</td>
<td>5.0 (0.7)</td>
<td>8.9 (2.8)</td>
<td>0.0006</td>
<td></td>
</tr>
<tr>
<td>$S_{PO_2}$ (%)</td>
<td>98.8 (1.6)</td>
<td>95.6 (9.3)</td>
<td>NS</td>
<td>98.8 (1.4)</td>
<td>74 (17)</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>$P_{aO_2}$ (kPa)</td>
<td>76.7 (10)</td>
<td>35.5 (14.5)</td>
<td>&lt;0.0001</td>
<td>21.3 (3.7)</td>
<td>11.7 (2.3)</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.46 (0.08)</td>
<td>7.34 (0.08)</td>
<td>0.0029</td>
<td>7.49 (0.07)</td>
<td>7.30 (0.10)</td>
<td>0.0022</td>
<td></td>
</tr>
<tr>
<td>$Hb$ (g dl$^{-1}$)</td>
<td>7.2 (0.7)</td>
<td>7.0 (0.9)</td>
<td>NS</td>
<td>7.2 (0.9)</td>
<td>7.0 (0.9)</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>
Table 2 Respiratory-dependent oscillations during cyclic R/D in macrocirculation (SAP, \(P_{aO_2}\)) and brain microcirculation (\(P_{brO_2}\), \(S_{brO_2}\), CBF) at \(FI_{O_2}\) 1.0 and 0.3. Data are presented as mean (SD). Comparisons between amplitudes (\(\Delta\)) at baseline and cyclic R/D were performed by the Mann–Whitney test. Amplitude \(\Delta\), peak-to-peak amplitude; CBF, cerebral blood flow; cyclic R/D, cyclic recruitment and derecruitment; \(FI_{O_2}\), fraction of inspired oxygen; \(P_{aO_2}\), arterial partial pressure of oxygen; \(P_{brO_2}\), cerebral subcortical partial pressure of oxygen; NS, non-significant; SAP, systolic arterial pressure; \(S_{brO_2}\), cerebral cortical haemoglobin oxygen saturation; \(S_{pO_2}\), peripheral haemoglobin oxygen saturation.

<table>
<thead>
<tr>
<th>(FI_{O_2})</th>
<th>1.0</th>
<th>Cyclic R/D</th>
<th>P-value</th>
<th>0.3</th>
<th>Cyclic R/D</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(P_{aO_2}) (kPa)</td>
<td>76.7 (10)</td>
<td>0.3 (0.1)</td>
<td>35.5 (14.5)</td>
<td>10.6 (8)</td>
<td>&lt;0.0001</td>
<td>21.3 (3.7)</td>
</tr>
<tr>
<td>SAP (mm Hg)</td>
<td>117 (20)</td>
<td>2.7 (0.6)</td>
<td>101 (10)</td>
<td>20 (9)</td>
<td>&lt;0.0001</td>
<td>119 (17)</td>
</tr>
<tr>
<td>(S_{pO_2}) (%)</td>
<td>98.8 (1.6)</td>
<td>0.1 (0.3)</td>
<td>95.6 (9.3)</td>
<td>1.9 (1.7)</td>
<td>&lt;0.0001</td>
<td>98.8 (1.4)</td>
</tr>
<tr>
<td>(P_{brO_2}) (kPa)</td>
<td>7.4 (2.2)</td>
<td>0.05 (0.04)</td>
<td>7.8 (4.1)</td>
<td>0.6 (0.4)</td>
<td>&lt;0.0001</td>
<td>5.3 (2)</td>
</tr>
<tr>
<td>(S_{brO_2}) (%)</td>
<td>53.8 (16)</td>
<td>3 (1.4)</td>
<td>69.2 (14.4)</td>
<td>4.1 (1.5)</td>
<td>NS</td>
<td>53.8 (19.6)</td>
</tr>
<tr>
<td>CBF (AU)</td>
<td>336 (144)</td>
<td>56 (49)</td>
<td>415 (171)</td>
<td>198 (176)</td>
<td>0.0433</td>
<td>335 (162)</td>
</tr>
</tbody>
</table>

Fig 1 Baseline measurements of systemic (\(P_{aO_2}\), AP) and cerebral parameters (\(P_{brO_2}\), CBF) over time. No dependency on the rate of respiration could be observed; AP, arterial pressure; CBF, cerebral blood flow; \(P_{aO_2}\), arterial oxygen partial pressure.

Fig 2 Respiratory-dependent oscillations in systemic (\(P_{aO_2}\), AP) and cerebral (\(P_{brO_2}\), CBF) oxygenation during cyclic R/D. AP, arterial pressure; CBF, cerebral blood flow; cyclic R/D, cyclic recruitment and derecruitment; \(P_{aO_2}\), arterial oxygen partial pressure; \(P_{brO_2}\), cerebral subcortical partial pressure of oxygen.
cerebral measurement parameters, as referenced to phase, are displayed in Figure 4. Linear models revealed that $P_{aO_2}$ oscillations and SAP variations showed dependency on cerebral measurement parameters (Table 3).

Discussion
The present study investigated the influence of cyclic R/D on arterial ($P_{aO_2}$), peripheral ($S_{pO_2}$), cerebral subcortical ($P_{brO_2}$), and cerebral cortical ($S_{brO_2}$) oxygenation and on CBF at $F_{O_2}$
1.0 or 0.3 in a porcine model of ALI. This study further investigated the influence of additional SAP variations caused by cyclic R/D on cerebral oscillations.

### SAP and \( P_{O_2} \) oscillations after lung injury

Spontaneous breathing or mechanical ventilation induce oscillations of arterial pressure that predominantly are generated by respiratory-dependent changes of pleural pressure and ventricular loading.\(^7\) In the present study, this phenomenon provoked physiological SAP variations at baseline that significantly increased during cyclic R/D. In contrast to SAP variations that are caused by pleural pressure changes, \( P_{O_2} \) oscillations are generated by varying alveolar shunt fractions during cyclic R/D. A recent study yielded similar \( P_{O_2} \) oscillations amplitudes to ours in lung-lavaged pigs,\(^6\) whereas former studies in rabbits showed higher amplitudes of 52 (5.2)\(^3\) and 38 (17) kPa.\(^18\) These differences in amplitudes might be explained by the fact that \( P_{O_2} \) amplitudes depend on the amount of cyclic R/D due to species differences in thoracic compliance and alveolar gas filling characteristics.\(^3\)\(^4\) A clinical study revealed intraoperative \( P_{O_2} \) alterations ranging 4.9–83.3 kPa during single-lung ventilation,\(^19\) presumably caused by cyclic R/D as a result of atelectasis. About 90% of all patients develop atelectasis and 10–15% of lung tissue collapses during routine anesthesia.\(^20\) However, lung collapse can reach about 50% of lung tissue leading to significant perioperative lung dysfunction. Formation of atelectasis usually is blunted by the use of a higher oxygen fraction (e.g. \( F_{O_2} \) 0.3–0.5) during routine anesthesia. Therefore, cyclic R/D and associated \( P_{O_2} \) oscillations during routine anesthesia cannot be easily monitored. Clinically available \( S_{O_2} \) monitors average over about several seconds (e.g. 10 s) and, therefore, alterations in \( S_{O_2} \) are blunted. \( P_{O_2} \) oscillations can also be missed when BGA is performed at different parts of the respiratory cycle.

### Influence of \( F_{O_2} \) on amplitudes of \( P_{O_2} \) and \( S_{O_2} \) oscillations

Monitoring of \( P_{O_2} \) and \( S_{O_2} \) oscillations depends on arterial oxygen content in blood. With the reduction in \( F_{O_2} \) from 1.0 to 0.3, the mean amplitude of \( P_{O_2} \) oscillations decreased while the mean amplitude of \( S_{O_2} \) oscillations increased (Fig. 3). Past studies have shown that higher \( F_{O_2} \) (>0.6) causes atelectasis after 5–15 min and thereby can increase the shunt fraction.\(^21\)\(^22\) However, cyclic R/D remained mostly unchanged in the present study as repetitive measurements at \( F_{O_2} \) 1.0 and 0.3 revealed reproducible values. In line with theoretical considerations, \( P_{O_2} \) oscillations should be monitored at higher blood oxygen content when a significant amount of dissolved oxygen is present. In contrast, oscillations of haemoglobin-bound oxygen (\( S_{O_2} \)) ideally should be monitored at lowered blood oxygen content (\( S_{O_2} <97\%\)). As the monitoring of \( S_{O_2} \) oscillations can be performed non-invasively using fast peripheral \( S_{O_2} \) measurement, this approach might be promising for the detection of \( S_{O_2} \) oscillations in the clinical setting. Fast \( S_{O_2} \) measurement might serve as a surrogate parameter for the monitoring of cyclic R/D in patients at risk (e.g. obesity, pneumocapnoperitoneum, ALI/ARDS). Additionally, other fast devices based on photo-spectrometry (e.g. Hamamatsu NlO-200) could also allow the detection of cyclic R/D attributed \( S_{O_2} \) oscillations.\(^16\)\(^23\)

### Transmission of \( P_{O_2} \) oscillations to the brain

Cyclic R/D attributed oxygen oscillations occurred in subcortical and cortical brain tissue. These cerebral oxygen oscillations were accompanied by CBF oscillations. Phase shifts in cerebral macro- and microvasculature are regarded as cerebral autoregulatory mechanisms to counter-regulate alterations in CBF caused by SAP variations.\(^24\)\(^25\) Whereas the classical phase shift between systemic circulation and CBF is −40 to −80°, one former near-infrared spectroscopy study revealed a phase shift to the cerebral microvascular level of 80–90°.\(^23\) O2C-device parameters (\( S_{O_2} \), CBF) in the present study showed prolonged phases (182–355°). At this level of circulation, perfusion is slowed down to enable capillary diffusion of oxygen and energy substrates.\(^26\) During intact cerebral autoregulation, \( P_{BrO_2} \) values should not change as CBF counteracts SAP variations.\(^27\)\(^28\) These considerations would suggest impairment of cerebral autoregulation during the present study as CBF regulation was not sufficient to maintain constant \( P_{BrO_2} \).\(^29\) However, in contrast to brain oxygen monitoring technologies (e.g. Licox) where \( P_{BrO_2} \) oscillations might not be detected because of the low temporal resolution, this study measured \( P_{BrO_2} \) at an ultrafast (10 Hz) temporal resolution. The issue of assessing \( P_{BrO_2} \) in view of cerebral autoregulation should be re-evaluated using fast oxygen-sensing technologies (e.g. 10 Hz) as of paramount clinical importance.

### Clinical impact of cerebral \( P_{O_2} \) oscillations

The impact of \( P_{O_2} \) and \( S_{BrO_2} \) oscillations caused by cyclic R/D on brain integrity remains unknown. In theory, brain oxygen oscillations could affect steady-state microvascular oxygen gradients.\(^30\) These cyclic alterations of cerebral oxygenation might promote neuronal immunomodulation or, in the case
of altered oxygen levels, intermittent cerebral hypoxia. Recent studies investigating chronic obstructive pulmonary disease and sleep apnoea syndrome and high-altitude research suggest that cyclically altered arterial oxygenation might have detrimental effects on brain integrity. The underlying mechanism for these entities is attributable to an increase in reactive oxygen species with associated tissue damage, leading to apoptotic neuronal death. In contrast, intermittent cerebral hypoxia has been shown to be protective in some experimental settings. The effect of intermittent hyperoxia on the brain remains unknown. However, current knowledge is limited, and no conclusions can be made about effects of cyclic R/D on organs.

Limitations
The present study has a number of limitations. Experimental lavage models simulate surfactant depletion and associated impairment of oxygenation, diffusion, and perfusion of the lung. Using this model, alveolar surface tension increases and significant atelectasis is produced. This leads to cyclic R/D during injurious mechanical ventilation. However, the model applied in the present experimental study was rather extreme, and is not transferrable to clinical conditions. It remains unknown if cyclic R/D results in alterations in PaCO2. In theory, PaCO2 oscillations caused by cyclic R/D should be small in amplitude. However, cerebral CO2 reactivity effects occur in a range of seconds to minutes and therefore might have biased the present results. Another problem of the present study is that cyclic R/D was not determined using more sophisticated techniques such as multiple inert gas elimination technique. Although results could be confirmed by repetitive measurements, it cannot be excluded that higher FiO2 of 1.0 had an effect on cyclic R/D and thereby PaO2 oscillation amplitude.

The relationship between systemic (PaO2, oscillations, SAP variations) and cerebral oscillations (PbrO2, SbrO2, CBF) should be investigated under more physiological conditions in view of cerebrovascular autoregulation. It would be interesting to confirm the present results using alternative cerebral imaging techniques such as functional magnetic resonance imaging to monitor cerebral P02 oscillations. Major technological confounders of the present study include accuracy, temporal synchronization, and porcine-specific alterations of the oxyhaemoglobin dissociation curve.

Conclusions
The present study demonstrates that cyclic R/D in an animal model of ALI induces respiratory-dependent systemic (PaO2) and peripheral (SpO2) oscillations. Fast photo-spectrometry may be a useful tool to monitor peripheral SpO2 oscillations non-invasively. PaO2 and SpO2 oscillations were transmitted to the cerebral microcirculation and could be monitored in subcortical (PbrO2) and cortical (SbrO2) cerebral tissue, and were accompanied by CBF oscillations. Our findings suggest that oscillation monitoring depends on haemoglobin–oxygen binding characteristics and underlying measurement technique. High temporal resolution oxygen-sensing technologies are required to detect cyclic R/D-associated oxygen oscillations. The impact of the cerebral transmission of PaO2 oscillations on the cerebral microcirculation remains unknown. This cyclic variation of systemic and cerebral oxygenation could play a major role in the crosstalk of acute lung and brain injury.

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Declaration of interest
None declared.

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