Extracorporeal Gas Exchange and Spontaneous Breathing for the Treatment of Acute Respiratory Distress Syndrome: An Alternative to Mechanical Ventilation?*

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*See also p. 758.

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**Objectives:** Venovenous extracorporeal gas exchange is increasingly used in awake, spontaneously breathing patients as a bridge to lung transplantation. Limited data are available on a similar use of extracorporeal gas exchange in patients with acute respiratory distress syndrome. The aim of this study was to investigate the use of extracorporeal gas exchange in awake, spontaneously breathing sheep with healthy lungs and with acute respiratory distress syndrome and describe the interactions between the native lung (healthy and diseased) and the artificial lung (extracorporeal gas exchange) in this setting.

**Design:** Laboratory investigation.

**Setting:** Animal ICU of a governmental laboratory.

**Subjects:** Eleven awake, spontaneously breathing sheep on extracorporeal gas exchange.

**Interventions:** Sheep were studied before (healthy lungs) and after the induction of acute respiratory distress syndrome via IV injection of oleic acid. Six gas flow settings (1–10 L/min), resulting in different amounts of extracorporeal CO₂ removal (20–100% of total CO₂ production), were tested in each animal before and after the injury.

**Measurements and Main Results:** Respiratory variables and gas exchange were measured for every gas flow setting. Both healthy and injured sheep reduced minute ventilation according to the amount of extracorporeal CO₂ removal, up to complete apnea. However, compared with healthy sheep, sheep with acute respiratory distress syndrome presented significantly increased esophageal pressure variations (25±9 vs 6±3 cm H₂O; p < 0.001), which could be reduced only with very high amounts of CO₂ removal (> 80% of total CO₂ production).

**Conclusions:** Spontaneous ventilation of both healthy sheep and sheep with acute respiratory distress syndrome can be controlled via extracorporeal gas exchange. If this holds true in humans, extracorporeal gas exchange could be used in awake, spontaneously breathing patients with acute respiratory distress syndrome to support gas exchange. A deeper understanding of the pathophysiology of spontaneous breathing during acute respiratory distress syndrome is however warranted in order to be able to propose extracorporeal gas exchange as a safe and valuable alternative to...
Extracorporeal gas exchange and spontaneous breathing for the treatment of acute respiratory distress syndrome: an alternative to mechanical ventilation?*
Venovenous extracorporeal gas exchange (ECGE), also called “extracorporeal membrane oxygenation,” is increasingly used as an adjunct to mechanical ventilation in patients with acute respiratory distress syndrome (ARDS) (1–4). Furthermore, ECGE has been successfully used in awake, nonintubated, spontaneously breathing patients as a bridge to lung transplantation (5–8) and is being used for the treatment of exacerbation of chronic obstructive pulmonary disease (9, 10).

The rationale for supporting gas exchange with ECGE alone, that is, without mechanical ventilation, in patients with ARDS is strong. Indeed, the avoidance of mechanical ventilation would have several advantages as it could potentially reduce the prevalence of ventilator-associated pneumonia and ventilator-induced lung injury. Furthermore, as the performance of active physical therapy was shown to be feasible while on ECGE (7, 11, 12), the reduction in depth of sedation allowed by the avoidance of mechanical ventilation could favor its performance. Nevertheless, limited data are available on the use of ECGE as an alternative to mechanical ventilation for ARDS patients (13), that is, for patients characterized both by acute impairment of \( \text{CO}_2 \) removal and severe hypoxemia.

If we consider the use of ECGE in awake, spontaneously breathing patients with ARDS, a new factor needs to be taken into account. Indeed, while the control of breathing has been thoroughly studied in physiological conditions and the key role of \( \text{CO}_2 \) has been identified (14, 15), less is known about the respiratory drive of ARDS patients. It is conceivable that neural pathways that are silent under physiological conditions—for example, bronchopulmonary C-fibers and other lung receptors (16, 17)—could be activated by lung edema, congestion, and inflammation and could influence the respiratory activity of patients with ARDS (18, 19).

The aim of the present work was to develop a model of awake, spontaneously breathing sheep on venovenous ECGE in order to study the interactions between the artificial and the native lung. We hypothesized that, in sheep with ARDS, gas exchange could be supported with ECGE alone and that spontaneous ventilation could be controlled via ECGE similarly to healthy sheep.

**Materials and Methods**

This study was approved by the U.S. Army Institute of Surgical Research Animal Care and Use Committee and was conducted in compliance with the Animal Welfare Act, the Implementing Animal Welfare Regulations, and in accordance with the principles of the Guide for the Care and Use of Laboratory Animals.

**Animal Preparation**

Under general anesthesia, 11 mixed-breed female sheep (45±6 kg) were tracheostomized. Catheters were placed in the right carotid artery and in the pulmonary artery (via left jugular vein). A balloon catheter (Ackrad Labs, Cooper Surgical, CT) was introduced transnasally in the esophagus (20) and respiratory system and lung pressure-volume (PV) curves were obtained, as previously described (21), starting from functional residual capacity. Chest CT (Toshiba Aquilion 64-slice Medical System, Tustin, CA) was performed (60 mAs, 120 kVp, pitch factor 0.85) at airway pressures of 0 and 30 cm H2O for lung quantitative analysis (Maluna 3.17, Göttingen, Germany) (22, 23). A 23F bicaval dual-lumen catheter (Avalon Elite, Maquet, Rastatt, Germany) was placed via right jugular vein as previously described (24) and connected to the Cardiohelp (Cardiohelp, Maquet, Rastatt, Germany). Blood flow (BF) through the membrane lung (ML) was set at 2 L/min and kept constant throughout the study. Activated clotting time was kept greater than 160 with heparin infusion. Midazolam (0.05–0.20 mg/kg/hr) and buprenorphine (0.01 mg/kg every 4–6 hr) were administered for sedation and analgesia. For each sheep, the level of sedation was kept constant throughout the study.

**Study: “Healthy Lungs”**

Sheep were placed prone, awakened, weaned from mechanical ventilation and kept, via tracheostomy, on continuous positive airway pressure (CPAP) of 8 cm H2O with \( \text{FiO}_2 \) of 0.5 (Evita XL, Dräger Medical, Germany). Control measurements were performed once the animals were stable (on average 180 min after instrumentation). Thereafter, six different sweep gas flows (GFs) (range, 1–10 L/min) and therefore different amounts of \( \text{CO}_2 \) removal by the ML (\( \text{V}_{\text{ml}}\text{CO}_2 \)) were randomly tested in each sheep (Table E1, Supplemental Digital Content 1, http://links.lww.com/CCM/A818); \( \text{FiO}_2 \) of GF was set at 0.5. Each setting was maintained for 30–40 minutes, at the end of which measurements were performed (Data Collection section). Every two steps, GF was zeroed to measure control conditions.

**ARDS Induction and Study: “ARDS”**

Once all measurements had been performed, \( \text{FiO}_2 \) was increased to 1.0 and ARDS was induced via IV oleic acid (OA) injection (0.1–0.15 mL/kg) (25, 26) with target \( \text{Pao}_2 \) less than 200 mm Hg. All GF settings were repeated in the same order of the “healthy study” and the same measurements were performed. Less time (15–20 min) was spent at 0 L/min of GF to avoid discomfort for the animals.

**Data Collection**

Respiratory variables, esophageal pressure variations (\( \Delta P_{es} \)), arterial and mixed-venous blood gases, hemodynamics, \( \text{VCO}_2 \) (CO2SMO, Novametrix, Wallingford, CT) and oxygen uptake (\( \text{VO}_2 \)) of the native lung (\( \text{V}_{\text{ICO}_2}, \text{V}_{\text{ICO}_2} \)), and \( \text{VMax Encore, Viasys, Yorba Linda, CA) were recorded for every GF setting} \( \text{VO}_2 \) of the ML (\( \text{V}_{\text{ICO}_2} \)) was measured at predefined GF settings (Table E1, Supplemental Digital Content 1, http://links.lww.com/CCM/A818). Pulmonary shunt fraction and physiologic dead space were calculated with standard equations. Blood chemistry and serum cytokines (interleukin
**Statistical Analysis**

Data are expressed as mean ± SD unless otherwise stated. Variables recorded before (healthy lungs) and after the induction of ARDS were compared via paired t test or signed rank sum test, as appropriate. Categories of extracorporeal CO\(_2\) removal were compared with one-way analysis of variance (ANOVA) or the Kruskal-Wallis test. Tukey or Dunn test were used for post hoc multiple comparisons. Two-way ANOVA was used to assess interactions between groups (healthy sheep vs ARDS) and categories of extracorporeal CO\(_2\) removal. A rank transformation was used for nonnormally distributed variables that did not pass the equal variance test. Slopes and intercepts of linear regressions were compared with the test for equality of slopes and intercepts, respectively. Statistical significance was defined as p value less than 0.05. Analysis was performed with SAS v9.2 (SAS, Cary, NC) and SigmaPlot v12.0 (Systat Software, San Jose, CA).

For additional details on the methods, see the online supplemental data (Supplemental Digital Content 1, http://links.lww.com/CCM/A818).

**RESULTS**

All sheep were placed uneventfully on ECGE and survived the injury. No ECGE-related complications were observed. During OA injection, a transient period (45–90 s) of apnea coupled

<table>
<thead>
<tr>
<th>TABLE 1. Quantitative Chest CT Scan Results of Healthy Sheep and Sheep With Acute Respiratory Distress Syndrome</th>
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<tbody>
<tr>
<td><strong>Quantitative CT results</strong></td>
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<tr>
<td>-----------------------------</td>
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<tr>
<td>Lung volume (mL)</td>
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<tr>
<td></td>
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<tr>
<td>Air volume (mL)</td>
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<td></td>
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<tr>
<td>Mean CT number (HU)</td>
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<tr>
<td>Hyperinflated tissue (%)</td>
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<td></td>
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<tr>
<td>Normally aerated tissue (%)</td>
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<tr>
<td></td>
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<tr>
<td>Poorly aerated tissue (%)</td>
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<tr>
<td></td>
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<tr>
<td>Nonaerated tissue (%)</td>
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<tr>
<td></td>
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<tr>
<td>Lung weight (g)</td>
</tr>
</tbody>
</table>

Airway pressure = airway pressure at which the scan was performed (either 0 or 30 cm H\(_2\)O), p = p value of the comparison between values of healthy sheep and sheep with acute respiratory distress syndrome, lung volume = total lung volume, air volume = total volume of air of the lung, mean CT number = mean CT number of the whole lung expressed in Hounsfield Units, hyperinflated tissue = mass of hyperinflated tissue (density between −901 and −1,000 HU), normally aerated tissue = mass of normally aerated tissue (density between −900 and −501 HU), poorly aerated tissue = mass of poorly aerated tissue (density between −500 and −101 HU), nonaerated tissue = mass of nonaerated tissue (density between −100 and +200 HU), lung weight = weight of the lungs expressed in grams. All compartments are expressed as percentage of total lung weight.
with a marked bradycardia followed by 10–15 minutes of rapid shallow breathing was observed in all sheep.

**Description of the Study Population Without ECGE**

The average lung and respiratory system PV curves of healthy sheep are shown in Figure 1.

Table 1 summarizes quantitative CT results before and after the induction of ARDS. Respiratory variables and gas exchange of healthy spontaneously breathing sheep and sheep with ARDS are reported in Table 2. All data were recorded at 2 L/min of BF (33% ± 9% of cardiac output) in the absence of sweep GF.

A significant increase in pulmonary pressure (16 ± 3 vs 21 ± 6 mm Hg; \( p = 0.003 \)) was observed after the induction of ARDS. Furthermore, a reduction in cardiac output (6.3 ± 1.1 vs 4.6 ± 1.5 L/min; \( p = 0.006 \)) and central venous (2 ± 5 vs –2 ± 5 mm Hg; \( p = 0.03 \)) and pulmonary occlusion pressure (7 ± 3 vs 4 ± 4 mm Hg; \( p = 0.03 \)) was recorded. These variations were likely due to intravascular hypovolemia induced by plasma leakage caused by OA (25) which explains also the increase in hemoglobin (9.9 ± 1.1 vs 12.0 ± 1.7 g/dL; \( p < 0.001 \)) and hematocrit (29.1% ± 4.3% vs 37.1% ± 4.2%; \( p < 0.001 \)). A significant reduction both in WBCs (4.1 ± 1.3 vs 1.0 ± 1.1 10^3/mL) and in plasma cytokines IL-1\( \beta \), IL-8, and IL-10 (Table 3) was recorded.

**Table 2. Respiratory Variables and Blood Gases of Spontaneously Breathing Sheep Without Extracorporeal Gas Exchange**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Healthy</th>
<th>Acute Respiratory Distress Syndrome</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory rate (breaths/min)</td>
<td>24±5</td>
<td>62±27</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Tidal volume (mL)</td>
<td>395±121</td>
<td>265±69</td>
<td>0.002</td>
</tr>
<tr>
<td>( \Delta P_{es} ) (cm H(_2)O)</td>
<td>6.1±2.8</td>
<td>24.7±8.7</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Minute ventilation (L/min)</td>
<td>9.8±3.6</td>
<td>170±6.9</td>
<td>0.008</td>
</tr>
<tr>
<td>Alveolar minute ventilation (L/min)</td>
<td>5.7±2.7</td>
<td>2.7±1.5</td>
<td>0.003</td>
</tr>
<tr>
<td>Dead space fraction</td>
<td>0.44±0.10</td>
<td>0.81±0.10</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Pulmonary shunt fraction</td>
<td>0.01±0.01</td>
<td>0.25±0.10</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>( V_{\text{CO}_2} ) (mL/min)</td>
<td>230±106</td>
<td>145±49</td>
<td>0.002</td>
</tr>
<tr>
<td>( V_{O_2} ) (mL/min)</td>
<td>185±63</td>
<td>189±83</td>
<td>0.41</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>7.41±0.04</td>
<td>7.30±0.08</td>
<td>0.002</td>
</tr>
<tr>
<td>( P_{aCO_2} ) (mm Hg)</td>
<td>40.5±3.9</td>
<td>470±10.0</td>
<td>0.02</td>
</tr>
<tr>
<td>( P_{aO_2} ) (mm Hg)</td>
<td>227±27</td>
<td>94±57</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>( P_{aCO_2}:F_{IaO_2} ) ratio</td>
<td>454±54</td>
<td>94±57</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Sao(_2) (%)</td>
<td>100±0</td>
<td>90±7</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Svo(_2) (%)</td>
<td>73±7</td>
<td>56±13</td>
<td>0.002</td>
</tr>
<tr>
<td>Base excess (mEq/L)</td>
<td>1.0±3.9</td>
<td>–3.0±6.1</td>
<td>0.008</td>
</tr>
<tr>
<td>Lactate (mmol/L)</td>
<td>2.1±1.5</td>
<td>3.4±2.6</td>
<td>0.14</td>
</tr>
</tbody>
</table>

\( p = \) value of the paired \( t \) test, \( \Delta P_{es} \) = swing of esophageal pressure (surrogate of pleural pressure variation), dead space fraction = physiologic dead space fraction, shunt fraction = fraction of venous admixture, \( V_{\text{CO}_2} \) = carbon dioxide removed through the native lung expressed in mL/min, \( V_{O_2} \) = oxygen consumption expressed in mL/min.

\( F_{IaO_2} \) was set at 0.5 for healthy sheep, while it was set at 1 after acute respiratory distress syndrome induction. Positive end-expiratory pressure was kept constant throughout the study at 8 cm H\(_2\)O.

**Interactions Between Native and Artificial Lung**

Figure 2A shows the response in terms of reduction in minute ventilation to different amounts of \( V_{M:\text{CO}_2} \) (expressed as percentage of total \( V_{\text{TOT}CO}_2 \)) of healthy sheep. A good correlation (\( r^2 = 0.74; \ p < 0.001 \)) was found between \( V_{M:\text{CO}_2} \) and reduction in minute ventilation. The equation of the overall regression (\( y = –3.6 + 0.94x \)) closely resembled the identity line.

Figure 2B shows the same graph for injured sheep. Also sheep with ARDS reduced their spontaneous breathing activity according to the amount of \( C_{O_2} \) removed extracorporeally (\( y = –24.0 + 1.1x; \ r^2 = 0.59; \ p < 0.001 \)), up to complete apnea when \( V_{M:\text{CO}_2} \) approached total metabolic \( C_{O_2} \) production.

When comparing linear regressions of healthy and injured animals, no significant difference was observed for slopes (\( p = 0.19 \)) while a significant difference was observed for the intercepts of the equations (\( p < 0.001 \)).

**Analysis by Categories of Extracorporeal \( C_{O_2} \) Removal**

Experimental points were divided in three categories of \( V_{M:\text{CO}_2} \) (1–60%, 61–80%, and 81–100%, expressed as percentage of \( V_{\text{TOT}CO}_2 \)), in order to analyze, for each group, the variations in respiratory variables and gas exchange in response to different
amounts of \( V_m^{CO_2} \). Furthermore, data obtained at 0 L/min of GF, that is, \( V_m^{CO_2} \) of 0 mL/min (0% of \( V_{TOT}^{CO_2} \)), were added to the analysis (when applicable) as a separate group. Results for healthy and injured sheep are reported in Tables 4 and 5, respectively.

By partitioning minute ventilation into its two components, tidal volume and respiratory rate, a slight difference between healthy and injured animals was found. Indeed, both respiratory rate variation (Fig. 3) and tidal volume variation (Fig. 4) differed significantly between the two groups.

For additional results, see the online supplemental data (Supplemental Digital Content 1, http://links.lww.com/CCM/A818).

**DISCUSSION**

We developed a model of awake, spontaneously breathing sheep on venovenous ECGE that allowed us to study the ventilatory response to different amounts of extracorporeal \( CO_2 \) removal both in healthy sheep and in sheep with OA-induced ARDS.

Previous studies, performed in similar experimental settings in healthy, spontaneously breathing lambs and sheep (14, 15), demonstrated the key role of extracorporeal \( CO_2 \) removal in the control of breathing. So far, however, no experimental data had been reported on the use of ECGE in spontaneously breathing animals with ARDS and on the interactions between the artificial lung and the native, diseased lung.

The response to different amounts of extracorporeal \( CO_2 \) removal was, in some respects, similar in healthy and diseased animals. Indeed, in both conditions sheep reduced minute ventilation progressively and accordingly to the amount of removed \( CO_2 \), up to complete apnea (Fig. 2). Furthermore, the response of healthy sheep was very similar to previous reports.

<table>
<thead>
<tr>
<th>Cytokines (ng/mL)</th>
<th>Healthy</th>
<th>Acute Respiratory Distress Syndrome</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1β</td>
<td>97 ± 46</td>
<td>66 ± 53</td>
<td>0.02</td>
</tr>
<tr>
<td>Tumor necrosis factor-α</td>
<td>38 ± 9</td>
<td>39 ± 11</td>
<td>0.20</td>
</tr>
<tr>
<td>IL-6</td>
<td>263 ± 274</td>
<td>211 ± 217</td>
<td>0.12</td>
</tr>
<tr>
<td>IL-10</td>
<td>382 ± 229</td>
<td>139 ± 182</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>IL-8</td>
<td>216 ± 235</td>
<td>67 ± 92</td>
<td>0.008</td>
</tr>
</tbody>
</table>

IL = interleukin.

Measurement of plasma cytokines was performed on a subset of animals (\( n = 8 \)) for technical problems related to plasma storage of the first 3 experiments. Comparison was performed with the paired \( t \) test. For additional details on the methodology used for cytokine analysis, see the online supplemental data (Supplemental Digital Content 1, http://links.lww.com/CCM/A818).

**TABLE 3. Plasma Cytokines in Healthy Sheep and in Sheep With Acute Respiratory Distress Syndrome**

![Figure 2. Correlation between extracorporeal \( CO_2 \) removal and reduction in minute ventilation in healthy sheep (A) and in the same sheep with acute respiratory distress syndrome (B). Extracorporeal \( CO_2 \) removal is expressed as percentage of total \( CO_2 \) production (\( V_{TOT}^{CO_2} = V_m^{CO_2} + V_L^{CO_2} \)), while minute ventilation is expressed as percentage reduction compared to control values, that is, measured minute ventilation in the absence of extracorporeal \( CO_2 \) removal. Every symbol (combination of shape and color) represents, in both panels, experimental points recorded from the same animal. The regression lines refer to the overall population.](http://links.lww.com/CCM/A818)
TABLE 4. Analysis by Categories of Extracorporeal CO₂ Removal in Healthy Sheep

<table>
<thead>
<tr>
<th>Healthy Sheep (n = 11)</th>
<th>Extracorporeal CO₂ Removal (% of Total VCO₂)</th>
<th>0%</th>
<th>1–60%</th>
<th>61–80%</th>
<th>81–100%</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>V̄v CO₂ % (%)</td>
<td>NA</td>
<td>43 ± 11&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>70 ± 6&lt;sup&gt;a&lt;/sup&gt;</td>
<td>91 ± 7</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Sweep gas flow (L/min)</td>
<td>NA</td>
<td>3.5 ± 3.1&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>7.1 ± 3.7</td>
<td>7.3 ± 3.7</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>V̄c CO₂ (mL/min)</td>
<td>NA</td>
<td>123 ± 61&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>180 ± 49</td>
<td>175 ± 35</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>V̄c CO₂ (mL/min)</td>
<td>230 ± 106&lt;sup&gt;abc&lt;/sup&gt;</td>
<td>158 ± 69&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>79 ± 32&lt;sup&gt;a&lt;/sup&gt;</td>
<td>18 ± 17</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>V̄c CO₂ (mL/min)</td>
<td>NA</td>
<td>281 ± 115&lt;sup&gt;a&lt;/sup&gt;</td>
<td>258 ± 76&lt;sup&gt;a&lt;/sup&gt;</td>
<td>193 ± 42</td>
<td>0.008</td>
<td></td>
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<tr>
<td>V̄c O₂ (mL/min)</td>
<td>185 ± 64&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>174 ± 102&lt;sup&gt;a&lt;/sup&gt;</td>
<td>124 ± 50</td>
<td>96 ± 54</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>V̄c O₂ (mL/min)</td>
<td>NA</td>
<td>227 ± 111&lt;sup&gt;a&lt;/sup&gt;</td>
<td>172 ± 55</td>
<td>145 ± 64</td>
<td>0.008</td>
<td></td>
</tr>
<tr>
<td>MV reduction (% of control)</td>
<td>NA</td>
<td>36 ± 17&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>60 ± 13&lt;sup&gt;a&lt;/sup&gt;</td>
<td>84 ± 14</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>MV reduc. (% of control)</td>
<td>NA</td>
<td>39 ± 21&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>65 ± 12&lt;sup&gt;a&lt;/sup&gt;</td>
<td>90 ± 8</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Tidal volume (mL)</td>
<td>395 ± 121&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>317 ± 96&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>231 ± 112&lt;sup&gt;a&lt;/sup&gt;</td>
<td>84 ± 65</td>
<td>&lt;0.001</td>
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<tr>
<td>∆P eso (cm H₂O)</td>
<td>6.1 ± 2.8&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>5.6 ± 2.5&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>3.2 ± 1.0</td>
<td>2.6 ± 2.0</td>
<td>&lt;0.001</td>
<td></td>
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<tr>
<td>Respiratory rate (breaths/min)</td>
<td>24 ± 5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>23 ± 5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>19 ± 6</td>
<td>11 ± 10</td>
<td>&lt;0.001</td>
<td></td>
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<tr>
<td>Pulmonary shunt fraction</td>
<td>0.01 ± 0.01&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>0.01 ± 0.00&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>0.03 ± 0.03</td>
<td>0.12 ± 0.17</td>
<td>&lt;0.001</td>
<td></td>
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<tr>
<td>Dead space fraction</td>
<td>0.44 ± 0.12&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.46 ± 0.11&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.52 ± 0.11&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.76 ± 0.19</td>
<td>&lt;0.001</td>
<td></td>
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<tr>
<td>PAO₂ (mm Hg)</td>
<td>227 ± 27&lt;sup&gt;a&lt;/sup&gt;</td>
<td>229 ± 39&lt;sup&gt;a&lt;/sup&gt;</td>
<td>214 ± 29</td>
<td>168 ± 64</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>PacO₂ (mm Hg)</td>
<td>40.5 ± 3.9</td>
<td>38.1 ± 4.3</td>
<td>37.3 ± 4.8</td>
<td>36.4 ± 4.6</td>
<td>0.13</td>
<td></td>
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<tr>
<td>Arterial pH</td>
<td>7.41 ± 0.04</td>
<td>7.45 ± 0.06</td>
<td>7.43 ± 0.05</td>
<td>7.46 ± 0.05</td>
<td>0.07</td>
<td></td>
</tr>
</tbody>
</table>

p = p value of the one-way analysis of variance, NA = not available, V̄v CO₂ % = amount of extracorporeal CO₂ removal expressed as percentage of total VCO₂, V̄c CO₂ = absolute value of extracorporeal CO₂ removal expressed in mL/min, V̄c O₂ = V̄c of the sheep, V̄c CO₂ = total VCO₂, V̄c O₂ = oxygen uptake of the sheep, V̄c CO₂ = total oxygen uptake (sheep + extracorporeal gas exchange), V̄c O₂ did not change with gas flow and was considered constant for each sheep), MV reduction = reduction in minute ventilation expressed as % of control values, MV reduc. = reduction in alveolar minute ventilation expressed as percentage of control values, ∆P eso = esophageal pressure swings (available in 10 animals).

<sup>p</sup> < 0.05 vs. 0%.
<sup>ab</sup> p < 0.05 vs. 1–60%.
<sup>a</sup> p < 0.05 vs. 61–80%.
<sup>b</sup> p < 0.05 vs. 1–60%.

Experimental measurements were divided into four categories of extracorporeal CO₂ removal: 0%, 1–60%, 61–80%, and 81–100%, expressed as percentage of total metabolic CO₂ production. The average value for each sheep of data obtained at 0 L/min of gas flow, that is, V̄v CO₂ of 0 mL/min (0% of V̄c CO₂), was used for analysis.

Data are expressed as mean ± sd.

(14, 15), with the overall regression equation being close to the identity line (Fig. 2A).

On the other hand, sheep with ARDS had a similar slope, but a significantly lower intercept (Fig. 2B). As the intercept of this graph represents the reduction in minute ventilation expressed as percentage of control (ventilation without ECGE), a negative value means that sheep with ARDS, on average, would have needed to breathe 20–25% more than their control ventilation to eliminate all metabolically produced CO₂. Furthermore, this means that 20–25% of total VCO₂ could be removed extracorporeally without a significant effect on minute ventilation. Above those values, pCO₂ and pH were normalized and sheep responded to increasing CO₂ removal by reducing ventilation, up to apnea. However, in injured animals, the response to CO₂ removal was more heterogeneous, with some animals presenting significant spontaneous ventilation despite high amounts of CO₂ unloading. This observation, which might be explained by the influence on spontaneous breathing of factors not directly linked to gas exchange (agitation, metabolic status, and lung receptor activity), might be of potential clinical relevance as it suggests that the response of individual patients could differ despite similar circumstances.

An increase in pulmonary shunt fraction was recorded in all animals for high amounts of extracorporeal CO₂ removal. This fact, which was likely caused by pulmonary derecruitment/atelectasis (14), might have been accentuated by high FiO₂ in sheep with ARDS. Lung derecruitment might not be tolerated by the sickest patients; however, it is conceivable that the application of higher levels of CPAP (27) or the use of biphasic positive airway pressure (28) could reduce/prevent its occurrence. Of note, injured sheep presented only moderate pulmonary shunt (25% ± 10%) despite the marked increase in pulmonary edema and the increase in poorly and nonaerated lung tissue (Table 1). This fact might be explained by some typical features...
Experimental measurements were divided into four categories of extracorporeal CO₂ removal: 0%, 1–60%, 61–80%, and 81–100%, expressed as percentage of total V̇CₐO₂. Two components of V̇CₐO₂, that is, V̇CₐO₂ = V̇CₐO₂ of the sheep, V̇CₐO₂ = oxygen uptake of the sheep, V̇CₐO₂ = total oxygen uptake (sheep + extracorporeal gas exchange), V̇CₐO₂ did not change with gas flow and was considered constant for each sheep. MV reduction = reduction in minute ventilation expressed as % of control values, MVA LV reduction = reduction in alveolar minute ventilation expressed as percentage of control values, ∆Pₑ = esophageal pressure swings (available in 10 animals). *p < 0.05 vs. 81–100%. **p < 0.05 vs. 61–80%.

Experimental measurements were divided into four categories of extracorporeal CO₂ removal: 0%, 1–60%, 61–80%, and 81–100%, expressed as percentage of total metabolic CO₂ production. The average value for each sheep of data obtained at 0 L/min of gas flow, that is, VM₂ = total oxygen uptake (sheep + extracorporeal gas exchange, VM₂ = absolute value of extracorporeal CO₂ removal expressed as percentage of total V̇CₐO₂, VM₂ = oxygen uptake of the sheep, VM₂ = total V̇CₐO₂, VM₂ = oxygen uptake of the sheep, VM₂ = total oxygen uptake (sheep + extracorporeal gas exchange), VM₂ did not change with gas flow and was considered constant for each sheep), MV reduction = reduction in minute ventilation expressed as % of control values, MVA LV reduction = reduction in alveolar minute ventilation expressed as percentage of control values, ∆Pₑ = esophageal pressure swings (available in 10 animals). *p < 0.05 vs. 81–100%. **p < 0.05 vs. 61–80%.

When analyzing the relative contribution of tidal volume and respiratory rate to the reduction in minute ventilation due to CO₂ unloading (Figs. 3 and 4), we found slightly different responses in healthy and injured sheep. In healthy sheep, the respiratory rate to the reduction in tidal volume decreased. However, in injured sheep, the reduction in minute ventilation was caused first by a reduction in tidal volume and only for higher values of V̇CₐO₂ also by of spontaneous breathing: preserved diaphragmatic activity and favorable ventilation/perfusion ratio (29).

High amounts of extracorporeal CO₂ removal were also associated to a significant increase in physiologic dead space, which was likely caused primarily by a relative increase in anatomic dead space fraction due to the reduction in tidal volume. Another possible factor contributing to the observed increase in physiologic dead space was the recorded increment in pulmonary shunt (30).

Another interesting finding was the analysis of the two components of V̇CₐO₂. On the one hand, oxygen delivery through the ML, that is, V̇CₐO₂, was constant throughout the study phases (no correlation with V̇CₐO₂) but increased significantly after ARDS induction (51 ± 18 vs 79 ± 17 mL/min; p < 0.001) due to increased hemoglobin concentration and reduced hemoglobin saturation of blood entering the ML (72% ± 8% vs 62% ± 10%; p < 0.001). On the other hand, a progressive and significant reduction in V̇CₐO₂ was observed with increasing V̇CₐO₂, resulting in a significant reduction in total oxygen consumption. The reduced oxygen consumption might be explained by a reduced respiratory muscle activity, that is, a lower cost of breathing (31). As a reduction in oxygen consumption also implies a lower CO₂ production, this effect could therefore potentially increase the relative contribution of ECGE. In our opinion, this “metabolic” effect of ECGE deserves attention, and its potential role in optimizing extracorporeal support needs to be defined, especially in patients supported with ECGE for longer periods.
Data are expressed as mean ± SE. while hatched bars represent sheep with acute respiratory distress syndrome. A two-way analysis of variance was performed (p = 0.001). Data are expressed as mean ± se.

Figure 3. Variations in respiratory rate (expressed as % of control measurements) caused by different amounts of extracorporeal CO₂ removal expressed as percentage of total CO₂ production. Experimental points were grouped in three categories of extracorporeal CO₂ removal: 1–60%, 61–80%, and 81–100%. Black bars represent healthy sheep, while hatched bars represent sheep with acute respiratory distress syndrome. A two-way analysis of variance was performed (p = 0.01). Data are expressed as mean ± se.

Figure 4. Variations in tidal volume (expressed as % of control measurements) caused by different amounts of extracorporeal CO₂ removal expressed as percentage of total CO₂ production. Experimental points were grouped in three categories of extracorporeal CO₂ removal: 1–60%, 61–80%, and 81–100%. Black bars represent healthy sheep, while hatched bars represent sheep with acute respiratory distress syndrome. A two-way analysis of variance was performed (p = 0.001). Data are expressed as mean ± se.

reduction in respiratory rate. On the contrary, in sheep with ARDS, the reduction in minute ventilation was caused first by a reduction in respiratory rate and only for higher values of VₐₕCO₂ also by a reduction in tidal volume.

Recorded tidal volumes without ECGE (GF = 0 L/min) were between 8 and 9 mL/kg in healthy sheep and between 5 and 6 mL/kg in sheep with ARDS. In fact, spontaneous tidal volumes recorded in sheep with ARDS could be considered “protective” for mechanical ventilation (32).

However, in injured animals at 0 L/min of GF, ΔPₓ (a surrogate for transpulmonary pressures) was 24.7 ± 8.7 cm H₂O, which corresponds to a dynamic variation in transpulmonary pressure very close to the one recorded in static conditions in healthy animals when inflating the lung from functional residual capacity to total lung capacity (Fig. 1). If we assume that the portion of the lung still viable for ventilation, that is, the “baby lung” (33), has similar anatomical and physiological characteristics of healthy alveoli, we might hypothesize that those lung units were subject to a deformation that approached their own total capacity and that they could therefore be potentially subjected to cellular stress failure (34). Indeed, several studies that investigated spontaneous hyperventilation, be it experimental (35, 36), exercise-related (37, 38), or clinical (39), discussed the potential role of spontaneous alveolar stretching in the development of pulmonary edema that in fact did not differ from ventilator-induced lung injury. We must therefore be very cautious in assuming that the risk of ventilator-induced lung injury could be eliminated through the use of ECGE and the avoidance of mechanical ventilation, as spontaneous ventilation per se could also be potentially injurious (“ventilation-induced lung injury”). Furthermore, it is very important to underline the fact that sheep with ARDS reduced esophageal pressure variations and tidal volume only when very high amounts of CO₂ (> 80% of total VCO₂) were removed extracorporeally.

It might be of interest to speculate on the mechanisms that caused these high pleural pressure swings and this response pattern to extracorporeal CO₂ unloading. On the one hand, due to edema accumulation and lower lung compliance, higher pleural swings were necessary to be able to ventilate the injured lung. On the other, it is conceivable that other factors, for example, lung receptor activity, were involved. Indeed, while the control of breathing has been extensively studied in physiological conditions (40, 41), less is known about pathological situations in which neural pathways that are usually silent in physiological conditions may be active (18, 19).

In the present study, we have not evaluated the activity of pulmonary receptors or vagal afferents; however, we clearly observed, a few seconds after the injection of OA, the clinical manifestations of the pulmonary chemoreflex, that is, apnea and bradycardia followed by rapid shallow breathing. These phenomena have been attributed to the simultaneous activation of bronchopulmonary C-fibers (J-receptors) (42, 43). It is therefore likely that, because of both direct chemical activation and the ensuing activation caused by lung congestion, collapse, and microembolization (44), the activity of unmyelinated pulmonary fibers and other lung receptors was increased throughout the second study phase (ARDS) (18).

The role of cytokines in the pathogenesis of OA-induced ARDS is still debated (45). Indeed, some studies reported an increase in cytokines (46, 47), while others did not show any significant variation (48). Interestingly, we observed a reduction in several plasma cytokines (Table 4). These results are difficult to explain and their interpretation is of pure speculative
nature: on the one hand, it is possible that OA induced cellular lysis (reduction in WBCs) with ensuing reduction in circulating inflammatory mediators; on the other hand, a "cytokine catching" effect of the ML might be hypothesized.

Some important limitations of the present study need to be mentioned. First, the intrinsic limitations of the OA model need to be kept in mind (45). Indeed, the fact that inflammation is not a clear feature of the OA model limits the clinical translatability of our results to human ARDS.

Furthermore, we need to point out the relative short duration of the observations once ARDS was induced. In fact, we studied only the acute phase of ARDS. We therefore do not know if other factors could have a role in determining the respiratory pattern and response to extracorporeal CO₂ removal in later stages of the disease.

In conclusion, the rationale to use ECGE for the treatment of ARDS in spontaneously breathing patients as an alternative to mechanical ventilation is strong as it would allow to avoid several mechanical ventilation–associated side effects. Indeed, ECGE could be used both as first-line treatment in nonintubated patients with ARDS and to accelerate the weaning process in already intubated patients with respiratory failure. The risks associated with ECGE, especially bleeding and membrane failure, however, need to be kept in mind. Finally, in this scenario, a somewhat new player, namely spontaneous breathing, would enter in the arena of the ICUs.

This study sheds light on some aspects of the use of venovenous ECGE in spontaneously breathing patients with ARDS, but a deeper understanding of the pathophysiology of spontaneous breathing during ARDS and of the potential harm caused by high pleural pressure variations is warranted in order to be able to propose ECGE as a safe and valuable alternative to mechanical ventilation for the treatment of patients with ARDS.

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