ProLUNG®: The Essentials

March 2013

This file is designed to provide the essential publications related to the clinical use of the ProLUNG® and ProLUNG Meter® for the removal of excess CO₂.

The complete list of publication related to this product can be found on our website: www.estor.it
Ventilation Induced Lung Injury (VILI) is a well described phenomenon where the mechanical stress of artificial ventilation causes further damage to the lung characterized by a pro-inflammatory response (biotrauma) and reduced lung compliance.

Protective ventilation with lower tidal volumes (6 mL/Kg) has been shown to improve survival and hospital discharge in patients undergoing mechanical ventilation. This is a landmark study since no other trial has conclusively shown that a treatment or therapy can significantly improvement in survival in ARDS patients. This highlights the importance of limiting acute lung injury induced by ventilation in these patients in order to improve overall outcome.

However, if tidal volume is reduced too much, there is a buildup of excessive CO₂ which leads to respiratory acidosis.
The “baby lung” concept originated as an offspring of computed tomography examinations which showed in most patients with acute lung injury/acute respiratory distress syndrome that the normally aerated tissue has the dimensions of the lung of a 5- to 6-year-old child (300-500g aerated tissue). The respiratory system compliance is linearly related to the “baby lung” dimensions, suggesting that the ARDS lung is not “stiff” but instead small, with nearly normal intrinsic elasticity. Initially we taught that the “baby lung” is a distinct anatomical structure in the non-dependent lung regions. However, the density redistribution in prone position shows that the “baby lung” is a functional and not an anatomical concept. This provides a rational for “gentle lung treatment” and a background to explain concepts such as barotrauma and volutrauma.

From a physiological perspective, the “baby lung” helps to understand ventilator-induced lung injury. In this context, what appears dangerous is not the VT/Kg ratio but instead the VT/“baby lung” ratio. The practical message is straightforward: the smaller the “baby lung”, the greater is the potential for unsafe mechanical ventilation.

Take Home Message: Even low tidal volumes of 6 mL/Kg may cause over-distension and VILI in some patients.
The use of total extracorporeal support (removal of carbon dioxide and delivery of oxygenation; extracorporeal membrane oxygenation; ECMO) for the treatment of respiratory failure was originally proposed in the early 70’s by Hill. The first enthusiastic reports raised the hope that a new therapy had become available for severe ARDS. The first multicentered, randomized trial to study the use of total extracorporeal support versus conventional therapy in adult patients with ARDS was published in 1974; the mortality in the total extracorporeal support group was 90% and was not significantly different from that of the control group.
The idea of partial support (removing only carbon dioxide, with little to no impact on oxygenation) was proposed in 1977 by Kolobow and Gattinoni. These authors suggested that applying only a few ventilator breaths at low volumes and low peak inspiratory pressures (“lung rest”) could prevent damage to the compromised lungs. They called this protective ventilatory strategy low-frequency positive-pressure ventilation (LFPPV). With this technique, oxygenation and removal of carbon dioxide were dissociated: oxygenation occurred predominantly through the lungs, and a variable portion of the carbon dioxide was removed through an artificial lung (extracorporeal carbon dioxide removal: ECCO2-R).

Describing this approach, Gattinoni proposed a “continuous model” to evaluate the technological aspects (type of pump, characteristics of the oxygenator, type and size of the catheter), the clinical aspects (kind of surgical approach) and the physiological performance (amount of oxygen transferred to the patient and of carbon dioxide removed from). Renal extracorporeal support provides a convenient and safe way of implementing this strategy. It is less invasive for the patient, and less complex for the clinician; however, it is unable to transfer oxygen to the patient. ECMO, although extremely invasive for the patients and complex for the clinician, is able to provide full oxygen transfer and carbon dioxide removal. LFPPV-ECCO2-R was proposed at an intermediate level with flow ranging between 500–1000 ml, a small pump, veno-venous bypass and a small double lumen catheter.
To understand how this medical device removes of CO₂, you must refer to the mechanisms involved in the transport of CO₂ in the blood. It is essential to remember that only 7% of the carbon dioxide present in the blood is transported to the lungs in the form of dissolved gas; meaning that in 100 mL of blood about 3.5 mL of CO₂ is transported in the form of dissolved gas.

In other words, the transport capacity per milliliter of blood of CO₂ is much greater than the transport capacity per milliliter of blood for O₂.
Rationale: How can I remove over 30% of the CO₂ treating less than 10% of the circulating blood volume?

The transport of CO₂ in the blood is:

- 7% in the free form that is dissolved in the plasma
- 23% bound to carbaminohemoglobin
- 70% in the form of bicarbonate ions

$$\text{CO}_2 + \text{H}_2\text{O} \leftrightarrow \text{H}_2\text{CO}_3 \leftrightarrow \text{H}^+ + \text{HCO}_3^-$$

The reversible binding of carbon dioxide with the water of the erythrocytes following the action of carbonic anhydrase is responsible for about 70% of the total transport of CO₂. The ProLUNG® system completely removes dissolved CO₂ thereby causing a leftward shift of the above chemical reaction.
Tidal hyperinflation may occur in patients with acute respiratory distress syndrome who are ventilated with a tidal volume (Vt) of 6 mL/Kg of predicted body weight develop a plateau pressure (Pplat) of 28 ≤ Pplat ≤ 30 cmH2O. The authors verified whether Vt lower than 6 mL/Kg may enhance lung protection and that consequent respiratory acidosis may be managed by extracorporeal carbon dioxide removal.

METHODS: Pplat, lung morphology computed tomography, and pulmonary inflammatory cytokines (bronchoalveolar lavage) were assessed in 32 patients ventilated with a Vt of 6 mL/Kg. Data are provided as mean ± SD or median and interquartile (25th and 75th percentile) range. In patients with 28 ≤ Pplat ≤ 30 cmH2O (n = 10), Vt was reduced from 6.3 ± 0.2 to 4.2 ± 0.3 mL/Kg, and Pplat decreased from 29.1 ± 1.2 to 25.0 ± 1.2 cmH2O (P < 0.001); consequent respiratory acidosis (PaCO2 from 48.4 ± 8.7 to 73.6 ± 11.1 mmHg and pH from 7.36 ± 0.03 to 7.20 ± 0.02; P < 0.001) was managed by extracorporeal carbon dioxide removal. Lung function, morphology, and pulmonary inflammatory cytokines were also assessed after 72 hours.

RESULTS: Extracorporeal assist normalized PaCO2 (50.4 ± 8.2 mmHg) and pH (7.32 ± 0.03) and allowed the use of Vt lower than 6 mL/Kg for 144 (84-168) hours.
Upon entry to the study, patients with a baby lung that was over-distended (open circles) had higher concentrations of damaging pro-inflammatory cytokines compared to patients with “normal” pressures (open diamonds). After 72 hours of extracorporeal CO₂ removal which allowed for the use of tidal volumes lower than 6 mL/Kg, the high levels of cytokines were reduced to the levels of controls (closed circles).

Therefore, the improvement of morphological markers of lung protection and the reduction of pulmonary cytokines concentration (P < 0.01) were observed after 72 hours of ventilation with Vₜ lower than 6 mL/Kg. No patient-related complications were observed.

**CONCLUSIONS**

Vₜ lower than 6 mL/Kg enhanced lung protection. Respiratory acidosis consequent to low Vₜ ventilation was safely and efficiently managed by extracorporeal carbon dioxide removal.
Hemodynamic and respiratory parameters were assessed at baseline (T0) and after 3 (T1), 12 (T2), 24 (T3), and 48 (T4) hours. No adverse events occurred. From baseline to 48 hours, pH values increased and partial pressure of CO₂ reduced. At the same time ventilator support was reduced, thereby mitigating barotrauma and risk of over-distension.

Therefore, the use of a low-flow device for the removal of CO₂ may be an important aid for patients with severe respiratory acidosis in association with conventional therapy during the perioperative period following lung transplantation.

Table 1. Hemodynamic and Blood Gas Analysis Data, Ventilator Setting During the Study

<table>
<thead>
<tr>
<th>Parameter</th>
<th>T0</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>T4</th>
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<tr>
<td>pH</td>
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<td>7.25</td>
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<td>PaCO₂ (mm Hg)</td>
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<td>69</td>
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<td>PaO₂/FiO₂</td>
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<td>PIP (cm H₂O)</td>
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<td>PEEP (cm H₂O)</td>
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<td>Vt (mL)</td>
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<td>RR (b/min)</td>
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<td>MAP (mm Hg)</td>
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<td>APm (mm Hg)</td>
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<tr>
<td>HR (r/min)</td>
<td>96</td>
<td>95</td>
<td>88</td>
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</tr>
</tbody>
</table>

PIP, peak inspiratory pressure; PEEP, positive end expiratory pressure; Vt, tidal volume; RR, respiratory rate; MAP, medium arterial pressure; APm, medium pulmonary artery pressure; HR, hearth rate.
The ProLUNG® system is minimally invasive, efficient and simple to use.

ProLung® advantages:
- Easy to assemble
- More resistant materials
The ProLUNG® system is composed of a ProLUNG Meter®, the ProLUNG® cartridge and the ESTORflow pump.
The ProLUNG Meter® is the first device that allows the management of gas concentrations in a system of CO₂ removal. The device allows the clinician, throughout the CO₂ removal treatment, to control the air flow, air temperature and continuously analyze the quantity of CO₂ being removed by the system.

Control and management of the air supply allows for an improved safety during the treatment, via the automation of various processes (maintenance of the fiber and monitoring the performance of the device) otherwise costly in terms of time for the medical and paramedical staff.

- Adjusts medical grade air flow within a range 0-15 L/min
- Measures extracorporeal VCO₂ expressed in mL/min
- Keeps dry the capillary lumen of the cartridge for ProLUNG® CO₂ removal
- Shows the CO₂ removed

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Control and management of the air supply allows for an improved safety during the treatment, via the automation of various processes (maintenance of the fiber and monitoring the performance of the device) otherwise costly in terms of time for the medical and paramedical staff.
A flow chart to understand the application of the ProLUNG® system.

While it may cause some anxiety, permissive hypercapnia is acceptable in patients so long as the blood pH does not exceed 7.25, indicative of respiratory acidosis. If this occurs, the ProLUNG® system is ideally suited to reduce the excessive levels of CO₂ that cause this elevated pH via extracorporeal hemofiltration, in order to allow the continued application of protective ventilation, which is known to improve survival.
INTRODUCTION. Ventilation-refractory hypercapnia may frequently occur in patients undergoing lung transplantation, during the surgical procedure because of one lung ventilation, or in the post-operative period in case of primary graft dysfunction (PGD). When conventional therapies like ventilator support, administration of inhaled nitric oxide (iNO) and intravenous prostacyclins are inadequate, additional extracorporeal gas exchange could be necessary to recover lung function. ProLUNG® is a new veno-venous low-flow extracorporeal device to remove carbon dioxide in patients with respiratory acidosis.

METHODS. On March and April 2012, a 27-year-old woman and a 28-year-old man underwent double sequential lung transplantation, both affected by cystic fibrosis. The first patient developed ventilation-refractory hypercapnia during the one lung ventilation in the operatory theatre; the men developed severe PGD in the postoperative period. The treatments already included ventilator and hemodynamic support, iNO, and prostaglandin E1, but when partial pressure of CO2 reached values greater than 90 mmHg with pH < 7.2 we started treatment with ProLUNG® to remove CO2, using a central double lumen catheter. Hemodynamic and respiratory parameters were assessed at baseline and during the treatment.

RESULTS. During the study we assisted to the hemodynamic parameters improvement with artery pressure increase, reduction in pulmonary and systemic resistances and progressive increase in cardiac index. The pH values gradually returned normal and partial pressure of CO2 was reduced. At the same time ventilator support was reduced, thereby mitigating biotrauma, barotraumas and the risk of volutrauma. In the case of PGD, the ProLUNG® was useful for the weaning from mechanical ventilation, too.

CONCLUSIONS. ProLUNG® did not need a specialized staff and no adverse events occurred during the treatment. Thanks to its low invasiveness and the absence of hemodynamic effects, in our initial experience, the use of ProLUNG® may be an important aid for patients with mild hypoxia, but severe respiratory acidosis, in association with conventional therapy during the perioperative period in lung transplantation. Furthermore it could be a useful device for the earlier weaning from mechanical ventilation, reducing the serious risk of lung infection in lung transplanted patients.

Electronic poster ESICM 2012, Lisbon

0235 - Extracorporeal carbon dioxide removal: a new low Flow venovenous device in lung transplantation

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