CO2 removal: Is a new simplified device could extended the indications?

Laurent Papazian, Samir Jaber

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In the present issue of the journal, Godet et al. [1] reported in an in vivo animal study including 15 pigs, the safety and feasibility use of a device based on a Prismaflex® platform in removing CO_2 from the blood, thus decreasing $PaCO_2$ and acidosis hypercapnia. The technique was based on a standard renal replacement therapy (RRT) platform (Prismaflex®) that can be easily implemented on existing devices. This strategy used a novel stand alone gas exchanger kit incorporating a hollow fiber chamber without any RRT hemofilter. Although, the authors evaluated the effects on a short term period (less than 2 hours) and reported the efficiency by decreasing blood CO_2, the effects on a long term period should be evaluated in both animal and human future studies especially in non-healthy lungs.

Invasive mechanical ventilation is lifesaving for patients with acute respiratory distress syndrome (ARDS). However, we know for about 30 years that positive pressure mechanical ventilation is able to create lung injuries and to worsen previous lung injuries (ventilator-induced lung injury; VILI). To minimize these VILI, it is generally recommended limiting tidal volume (VT) to 6 mL/kg of predicted body weight and plateau pressure less than 30 cmH_2O. However, evidence is accumulating that it may not be fully protective against VILI and the less positive pressure ventilation is given, the less VILI are created. The price to pay this limited VT is a reduction of minute ventilation even if respiratory rate is increased, leading a respiratory hypercapnia so called ''permissive hypercapnia''. The first extracorporeal CO_2 removal ($ECCO_2R$) devices were designed 40 years ago. The technique never entered into clinical practice, probably because high blood flows were necessary, extracorporeal circuits were not biocompatible, large catheters were used and full anticoagulation was required.

$ECCO_2R$ is capable of eliminating at least 50% of the calculated CO_2 production, with rapid normalization of respiratory acidosis. This has led to the attempt of this technique in patients presenting with acute hypercapnic respiratory failure (COPD patients, bridge to transplant lung patients) [2]. $ECCO_2R$ systems are now proposed to reduce invasiveness of mechanical ventilation and, therefore, VILI in ARDS patients [3–7].

The older systems were driven by the arterio-venous pressure gradient; thus, cannulation of an arterial vessel (usually the femoral artery) was necessary for driving the system. Recent pump-driven veno-venous systems have been designed and are able to improve respiratory acidosis without requiring arterial cannulation. There are also some attempts to adapt continuous renal replacement devices to be able to clear CO_2 by specially designed filters. Clinical experience suggests that high flow rates are needed to correct severe respiratory acidosis ($pH < 7.2$). In this regard, the physiological relationships between cannula size, blood flow, sweep gas flow and gas transfer capacity, respectively, still remain largely unknown. For this reason, more physiological data on these issues are needed before the promising technique of miniaturized veno-venous $ECCO_2R$ can be tested in randomized controlled trials (RCTs) aiming to evaluate the possible beneficial clinical impact. Recently, a porcine study [7] indicated that pump-driven veno-venous $ECCO_2R$ required a blood flow of 750 to 1000 mL/min to normalize pH values and reduce $PaCO_2$ in severe life-threatening respiratory acidosis under constant ventilatory support. Therefore, using low-diameter catheters and low blood flow rates, pump-driven veno-venous $ECCO_2R$ may be primarily feasible in patients with mild to moderate respiratory acidosis. This may be aimed at reducing aggressiveness of invasive ventilation in patients with ARDS. Recently Grasso et al. [6] showed that the use of $ECCO_2R$ permitted to reduce respiratory rate from 30 to 14 breaths/min while removing 39% of CO_2 production. Interestingly some cytokines (interleukin-6 and tumor necrosis factor-α) concentrations were significantly lower in plasma and in bronchoalveolar lavage, suggesting that $ECCO_2R$ is also capable to limit biotrauma.

Since intensive care specialists are familiar with hemodialysis catheters, it is necessary to test whether these catheters also qualify for $ECCO_2R$. The maximal blood flow through these catheters is usually restricted to approximately 400 mL/min. Furthermore, catheters specifically designed for $ECCO_2R$ aim to avoid recirculation (PCO_2 of the venous blood, which is directed towards the oxygenator, is lower than arterial PCO_2). Recirculation was obvious when hemodialysis catheters were used, even with low blood flow [7]. Recirculation has not been evaluated in the Godet et al. study [1].

Using a pumpless extracorporeal lung assist, Bein et al.'s [4] randomized 79 ARDS patients were enrolled to receive a low VT ventilation (3 mL/kg) combined with extracorporeal CO_2 elimination, or to a ARDS-Net strategy (6 mL/kg) without the extracorporeal device. Ventilator-free days (VFD) within 60 days were not different between the two groups. However, in the more hypoxemic patients ($PaO_2/FIO_2 < 150$ mmHg) VFD-60 was higher in the $ECCO_2R$ group suggesting that next trials should focus on this moderate to severe ARDS group [4].

The concept of $ECCO_2R$ evolved in response to early trials of ECMO where the high incidence of adverse events and mechanical complications relegated the therapy to only the sickest of patients as a last ditch effort [4,8,9]. Furthermore, the high cost and complexity of the extracorporeal membrane oxygenation (ECMO) systems limited their use to a small number of high volume

specialized medical facilities. As the technology and understanding of extracorporeal gas exchange has improved, further reductions in the incidence of adverse events and mechanical failures have been achieved by:

- advances in hollow fiber membrane technology, in terms of reductions in the fiber diameter and wall thickness, and prevention of plasma leakage to reduce the need for gas exchanger replacements;
- more sophisticated arrangements of hollow fiber membranes which reduce priming volume, reduce resistance to both blood and sweep gas flow through the device, and improve the gas exchange efficiency allowing for reduced fiber surface area and/or circuit flow rate;
- the use of centrifugal pumps or non-occlusive pressure controlled roller pumps, which reduces damage to the blood (hemolysis) and the incidence of circuit rupture;
- biocompatible coatings on the fibers and circuit components (such as heparin), which reduce the risk of clot formation as well as the necessary levels of systemic anticoagulation;
- the use of single dual-lumen catheters and percutaneous venous cannulation, which reduces the incidence of cannulation-associated adverse events as well as the level of patient discomfort;
- simplifications in the system design to reduce risk of mechanical failure and operator error;
- use of active mixing of blood adjacent to the fibers to increase gas exchange efficiency, which allows for reduced fiber surface area and/or reduced blood flow;
- use of arterial-to-venous cannulation to eliminate the need for a pump.

Finally, the study of Godet et al. [1] showed that a simple technique based on a standard RRT platform (Prismaflex®) could be easily implemented on existing devices. In the future, such a device could be used associated with the lung protective or ultra-lung protective ventilation in more ICU patients in extended indications.

Disclosure of interest

Conflict of interest of Samir JABER: Dr Jaber reports receiving consulting fees from Dräger, Hamilton, Maquet and Fisher Paykel

Conflict of interest of Laurent PAPAZIAN: Laurent PAPAZIAN do not have any conflicts of interest to declare regarding this manuscript.

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Laurent Papazian[a,*,b]

[a]*Intensive care unit "acute respiratory failure and severe infections", Assistance publique–hôpitaux de Marseille, CHU Nord, 13015 Marseille, France*

[b]*Faculté de médecine, Aix-Marseille university, URMITE UMR CNRS 7278, 13005 Marseille, France*

Samir Jaber[c]

[c]*Intensive Care Unit and Transplantation, Critical Care and Anesthesia Department (DAR B), Saint-Eloi Hospital, University of Montpellier, INSERM U1046, CNRS UMR 9214, 34295 Montpellier cedex 5, France*

*Corresponding author

E-mail address: laurent.papazian@ap-hm.fr (L. Papazian)