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SPECIAL ISSUE INSIGHT

Physiology of extracorporeal CO_2 removal

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Extracorporeal CO_2 removal ($ECCO_2R$) was introduced in 1977 to control arterial CO_2 tension and reduce ventilation [1], thus allowing lung rest in patients with acute respiratory failure (ARF) [2].

Its feasibility has been tested in a clinical trial [3], but clear evidence of benefit is lacking. Furthermore, a recent randomized study comparing standard lung protective ventilation versus an ultra-protective strategy with $ECCO_2R$, in moderate-severe ARF, showed no difference in 90-day survival, but greater adverse events and fewer ventilator-free days in the $ECCO_2R$ arm [4]. Unfortunately, the relative contribution of $ECCO_2R$ on total CO_2 clearance and its effects on the natural lung are unexplored. Indeed, the CO_2 excretion from artificial and natural lungs is generally not measured, and the ventilatory strategy does not account for the physiological changes due to $ECCO_2R$. In this brief report, we aim to describe the physiological basis of CO_2 removal, extensively studied in healthy animal models. To which extent these concepts might be directly translatable to pathological conditions will require further clinical studies. However, a reappraisal of the physiological basis of $ECCO_2R$–natural lung interactions may clarify the rationale behind its clinical application.

Physical–chemical characteristics of $ECCO_2R$

The key concept underlying low-flow $ECCO_2R$ is that due to the high CO_2 content in the venous blood (45–50 ml/100 ml at venous $PCO_2 = 45$ mmHg), the metabolically produced CO_2 (~150–200 ml/min) may be theoretically removed from 400 to 500 ml of blood. The amount of CO_2 removed—for a given sweep gas flow—increases linearly with the artificial lung surface area and the PCO_2 of the pre-membrane blood; and logarithmically with the blood flow [5]. High ventilation/perfusion ratio of the artificial lung is required for an adequate CO_2 removal with a post-membrane PCO_2 as low as 5–10 mmHg [6].

Artificial and natural lung interactions

Physiology

The $ECCO_2R$ was first studied in healthy lambs [1]. The key-finding was that the sum of VCO_2 of the natural and artificial lungs remained unchanged when $ECCO_2R$ was increased. Consequently, the spontaneously breathing animals maintained a normal arterial PCO_2. When 100% of the metabolic VCO_2 was removed by the membrane lung, it was possible to maintain the animals "apneic" with normal PCO_2, while the oxygenation was maintained through an intratracheal 100% oxygen inflow matching the oxygen consumption ("apneic oxygenation") [7] (Fig. 1). A similar linear decrease in minute ventilation proportional to the $ECCO_2$-R was described in spontaneously breathing patients with ARF [8].

Gas exchange

1. While the amount of oxygen exchanged through the natural lung is unmodified by $ECCO_2R$, as the oxygen added extracorporeally is negligible, the VCO_2 eliminated by the natural lung decreased in proportion to the VCO_2 eliminated through $ECCO_2R$. Therefore, the respiratory quotient ($RQ = VCO_2/VO_2$) decreases. The change in RQ modifies the alveolar PO_2 which is function of both FiO_2 and the PCO_2/RQ ratio, according to the alveolar gas equation. Therefore, during $ECCO_2R$, despite a constant FiO_2, the alveolar and arterial PO_2 may decrease due to a decrease in RQ [7, 9]). The cardiovascular effects of $ECCO_2R$ will depend on the net effect on

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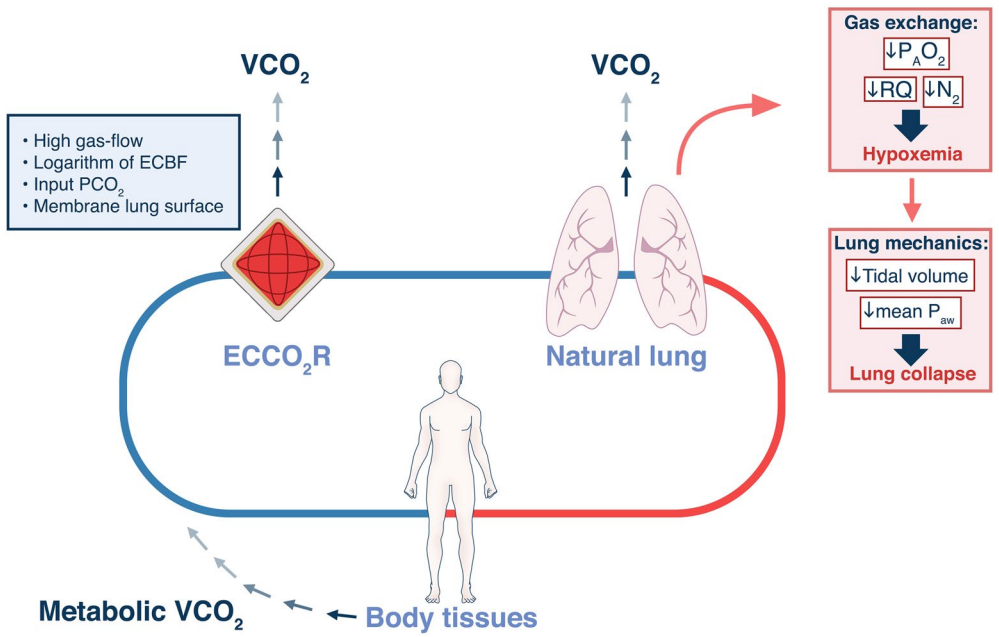

Fig. 1 Physiology of $ECCO_2R$: The amount of CO_2 removed (VCO_2) by the membrane lung is proportional to the gas-flow, the logarithm of extracorporeal blood-flow; the pre-membrane PCO_2 and the membrane lung surface. The sum of the VCO_2 of the membrane and the natural lungs, at equilibrium, equals the metabolic VCO_2. A reduction in the VCO_2 of the natural lung decreases the respiratory quotient (RQ) and, therefore, alveolar PO_2 (PAO_2). The alveolar nitrogen may decrease if the membrane lung is ventilated with fractions of oxygen higher than those delivered to the natural lung. The decrease of VCO_2 of the natural lung allows the decrease in tidal volume and mean airways pressure, which can promote lung collapse

the pulmonary vascular resistance resulting from the reduction in alveolar and arterial PO_2, and hypercapnia (increase in pulmonary arterial pressure); and the PO_2 and PCO_2 in the mixed venous blood which results from the extracorporeal support.

2. During apnea, the alveolar gas composition is affected by the nitrogen concentration in the artificial lung, to which the alveolar nitrogen equilibrates. If the nitrogen in the artificial is lower than the natural lung, i.e., if the fraction of oxygen delivered through the membrane lung is greater than FiO_2, the natural lung will be progressively depleted of nitrogen [7]. This may favor reabsorption atelectasis in the regions of the natural lung with low ventilation/perfusion ratio, increasing the pulmonary units instability [10]. This phenomenon was proved experimentally in conditions of apnea but may theoretically occur regionally during clinical conditions.

Lung mechanics

As tidal volume is reduced, the mean transpulmonary pressure decreases, and the lung tends to collapse. Experimental data on healthy animals show that the lung volume is halved after 24 h of apnea at 5 cmH_2O of positive end-expiratory pressure (PEEP) [7]. To prevent this phenomenon in healthy lungs, two alternatives are possible:

1. Raising the mean airway pressure. It must be noted, however, that a PEEP of ~ 20–25 cmH_2O may be required to preserve lung volumes in lambs during apnea [11], as well as to keep the lungs fully open in patients with acute respiratory distress syndrome (ARDS) [12]. These pressures are generally associated to important hemodynamic consequences, worse fluid balance and kidney function.
2. Adding an adequate short inflation "sigh". In healthy animals, it is sufficient to add one sigh of 10–12 ml/kg every 90 s to preserve lung volumes [13]. The role of sigh, in this context, is not to increase gas exchange, but only to preserve lung-volume [14, 15].

Discrepancies between physiology and actual current $ECCO_2R$ applications

Gas exchange

The effects of the decrease in respiratory quotient (RQ) during $ECCO_2R$ is usually ignored in clinical practice. However, this phenomenon may be relevant when FiO_2 is reduced, as during weaning. In this phase, the low RQ may cause hypoxemia, which may be incorrectly interpreted as caused by derecruitment.

The reabsorption atelectasis resulting from the lung de-nitrogenization when using 100% oxygen through the artificial lung may occur in the ARDS lung due higher

prevalence of low ventilation/perfusion regions, the higher weight of the lung, and the loss of diaphragmatic tone which favors the formation of compression atelectasis. This problem may be prevented by ventilating the artificial and natural lungs with the same oxygen fraction.

Lung mechanics

During "ultraprotective" lung strategy and $ECCO_2R$, PEEP is usually increased, and plateau pressure decreased, while the respiratory rate is maintained constant. Actually, in the intervention group of the REST trial, the mechanical ventilation was very similar to the controls [4]. The potential advantages of $ECCO_2R$ on mechanical ventilation were, therefore, not exploited, leading only to an increase in the complications associated to $ECCO_2R$ and anticoagulation. During ultraprotective ventilation strategy, three conditions may promote atelectasis: (a) lower tidal volume and plateau pressure; (b) lung de-nitrogenization when using 100% oxygen through the artificial lung; c) PEEP levels insufficient to keep the lung open ($\geq$ 20–25 cmH_2O). A combination of low frequency plus the addition of sighs and equal FiO_2 in the natural and artificial lungs—as suggested by physiology—could enhance lung protection and prevent progressive lung collapse.

Take-home message

Understanding the physiology of $ECCO_2R$ and the consequent modification in the natural lung is necessary to optimize the ventilatory management and design stronger future clinical trials.

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Declarations

Conflicts of interest

LG reports a consultancy for General Electrics and SIDAM. He also receives lecture fees from Estor and Mindray.

Ethical approval

Not requested.

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