Extracorporeal CO₂ removal (ECCO₂R) was introduced in 1977 to control arterial CO₂ 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 ECCO₂R, in moderate-severe ARF, showed no difference in 90-day survival, but greater adverse events and fewer ventilator-free days in the ECCO₂R arm [4]. Unfortunately, the relative contribution of ECCO₂R on total CO₂ clearance and its effects on the natural lung are unexplored. Indeed, the CO₂ excretion from artificial and natural lungs is generally not measured, and the ventilatory strategy does not account for the physiological changes due to ECCO₂R. In this brief report, we aim to describe the physiological basis of CO₂ 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 ECCO₂R–natural lung interactions may clarify the rationale behind its clinical application.

Physical–chemical characteristics of ECCO₂R

The key concept underlying low-flow ECCO₂R is that due to the high CO₂ content in the venous blood (45–50 ml/100 ml at venous PCO₂ = 45 mmHg), the metabolically produced CO₂ (~150–200 ml/min) may be theoretically removed from 400 to 500 ml of blood. The amount of CO₂ removed—for a given sweep gas flow—increases linearly with the artificial lung surface area and the PCO₂ 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 CO₂ removal with a post-membrane PCO₂ as low as 5–10 mmHg [6].

Artificial and natural lung interactions

Physiology

The ECCO₂R was first studied in healthy lambs [1]. The key-finding was that the sum of VCO₂ of the natural and artificial lungs remained unchanged when ECCO₂R was increased. Consequently, the spontaneously breathing animals maintained a normal arterial PCO₂. When 100% of the metabolic VCO₂ was removed by the membrane lung, it was possible to maintain the animals “apneic” with normal PCO₂, 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 ECCO₂R 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 ECCO₂R, as the oxygen added extracorporeally is negligible, the VCO₂ eliminated by the natural lung decreased in proportion to the VCO₂ eliminated through ECCO₂R. Therefore, the respiratory quotient (RQ = VCO₂/VO₂) decreases. The change in RQ modifies the alveolar PO₂ which is function of both FiO₂ and the PCO₂/RQ ratio, according to the alveolar gas equation. Therefore, during ECCO₂R, despite a constant FiO₂, the alveolar and arterial PO₂ may decrease due to a decrease in RQ [7, 9]). The cardiovascular effects of ECCO₂R will depend on the net effect on
the pulmonary vascular resistance resulting from the
reduction in alveolar and arterial PO2, and hypercapnia
(increase in pulmonary arterial pressure); and
the PO2 and PCO2 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 FiO2, 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 condi-
tions of apnea but may theoretically occur region-
ally during clinical conditions.

Lung mechanics
As tidal volume is reduced, the mean transpulmonary
pressure decreases, and the lung tends to collapse. Experi-
mental data on healthy animals show that the lung vol-
ume is halved after 24 h of apnea at 5 cmH2O of positive
depend-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 cmH2O 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
with 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 ECCO2R applications
Gas exchange
The effects of the decrease in respiratory quotient (RQ)
during ECCO2R is usually ignored in clinical practice.
However, this phenomenon may be relevant when FiO2
is reduced, as during weaning. In this phase, the low RQ
may cause hypoxemia, which may be incorrectly inter-
preted 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 ECCO₂R, 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 ECO₂R on mechanical ventilation were, therefore, not exploited, leading only to an increase in the complications associated to ECO₂R 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 (≥ 20–25 cmH₂O). A combination of low frequency plus the addition of sighs and equal FiO₂ 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 ECO₂R 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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