In 1973, Tilney et al. described, in 18 patients with a ruptured aortic aneurysm, a “sequential system failure” as the cause of death for 17 of them. Although apparently not involved by the primarily vascular pathology, lung and kidney were among the most represented failing organs. The modern definition of clinical syndrome as defined by Tilney et al. is multiorgan failure (MOF). MOF is “a progressive dysfunction of two or more organ systems following an acute threat to systemic homeostasis” and, similar to the description by Tilney et al., lungs and kidneys frequently are involved. Recent data have suggested that up to 60% of patients with MOF, receiving respiratory support, also need renal replacement therapy (RRT). On the other hand, patients who develop severe acute kidney injury (AKI) are exposed to an increased risk of death owing to extrarenal complications such as respiratory impairment, pulmonary congestion (fluid overload), and increased vascular permeability into the alveoli. At the same time, it has been shown that mechanical ventilation (MV) itself negatively influences kidney function: hemodynamic repercussions, biohumoral effects (including imbalance in innate immune/inflammatory response and oxidative stress), blood gas disorders, and biotrauma (see later) are among the principal players of this organ cross-talk. In modern intensive care units (ICUs), when organ dysfunction occurs, the primary clinical management is based on organ support until recovery while specific therapies (eg, antibiotics) are acting. It also has been recognized that complications, burdening patients’ morbidity and mortality, may result from these supporting interventions and ventilator-induced lung injury is the most frequent and studied of them. This awareness has led to the development of extracorporeal systems aimed at supporting pulmonary function in combination or alternatively to MV. Today, because of the growing severity of illness of critically ill patients, the combination of renal and respiratory support with extracorporeal systems is becoming a frequent occurrence in the ICU. This review focuses on theoretical and practical applications of renal-pulmonary support, touching on technical aspects of the most recent materials and devices.

**FROM VENTILATOR-INDUCED LUNG INJURY TO RESPIRATORY DIALYSIS**

Ventilator induced lung injury and protective ventilation

Since 1952, after the polio epidemic in Copenhagen, MV progressively has become routine practice in
emergency departments and ICUs to optimize gas exchange by positive pressure ventilation while respiratory muscles are maintained at rest. During the last 15 years, thanks to the contribution of a landmark trial in patients with acute respiratory distress syndrome (ARDS), the awareness that MV may further worsen already injured lungs has been consolidated, leading to the modern concept of protective ventilation (PV). More recently, it has emerged that even noninjured lungs may benefit from less aggressive ventilation strategies that ultimately lead to less pulmonary damage and complications. Ventilator-induced lung injury occurs when the ventilator delivers high volumes and high transpulmonary pressure (barotrauma), alveolar overdistension (volutrauma), and repetitive opening and closing of alveoli (atelectrauma). In addition to physical stress, MV induces the release of inflammatory mediators resulting in local and systemic inflammatory reaction (biotrauma) that negatively affects distal organs, promoting the development of multiorgan dysfunction. Clinical studies have shown that higher levels of inflammatory cytokines (eg, tumor necrosis factor [TNF]-α, and interleukin [IL]-1β, IL-6, and IL-8) are released into the alveoli and plasma in patients ventilated at conventional lung volumes compared with patients treated with a lung-protective strategy. A follow-up analysis of these patients showed that patients ventilated with higher tidal volume had higher rates of renal failure, and that the degree of MOF correlated with IL-6 levels. The recognition of these harmful MV effects on both healthy and diseased lungs, and the evidence of organ cross-talk leading to MOF, has led to a profound change in the approach to MV with low tidal volumes (6-8 mL/kg predicted body weight) and limited airway pressures (<25 to 30 cmH2O) as standard of practice. When PV is unable to maintain normal values of partial pressure of carbon dioxide in arterial blood (Paco2), the so-called permissive hypercapnia (PHC) is advised. PHC, was first shown to reduce injury in patients with severe asthma and, successively, in other clinical conditions and patient populations including infants, children, and adults. Although PHC has proven advantages and benefits, it may exert multiple negative effects, especially if coupled with metabolic acidosis, on different organs and systems: it may increase cerebral blood flow, which can be deleterious in cases of reduced intracranial compliance, hinder the lung epithelial and cellular repair after a stretch-induced injury, and exert immunosuppressive effects limiting the host response to microbial infection.

From permissive hypercapnia to extracorporeal carbon dioxide removal systems (ECCO2R)

To limit excessive CO2 accumulation and regional alveolar hyperinflation that, despite PV, still may occur in patients with ARDS, devices for extracorporeal CO2 removal (ECCO2R) have been developed. The first application of ECCO2R dates more than 30 years ago. It was first developed byGattinoni et al in the 1980s, however, because of the high incidence of complications, it did not initially achieve wide clinical use.

The general concept of an ECCO2R system is very close to a hemofiltration circuit: the blood is drained from the patients, CO2 is removed by a membrane, and blood then is re-injected into systemic circulation. Early examples of CO2 removal were attempted through hemodialysis: it is well known that only 5% of total CO2 is in gaseous form at normal pH and that HCO3 is easily removable through hemodialysis, with a clearance close to that of urea, without the requirement of high blood flow rates. Isobe et al ran a hemodialysis session on 6 anesthetized and apneic mongrel dogs weighing approximately 10 kg with a blood flow rate of 15 mL/kg/min thorough a 2-m2 hemodialyzer with a dialysate of 500 mL/min: to recirculate the dialysate, the effluent part of the circuit was added with a bubbling chamber where HCl was infused to react with cleared HCO3 and allow its elimination as CO2. With this model, they were able to achieve a CO2 clearance of more than 4 mL/kg/min, significantly reducing animals’ CO2 levels. On the backside, they were obliged to administer, during the 5-hour experiment, approximately a liter of Trometamol; tris-hydroxymethyl aminomethane (THAM) to compensate for anion loss. Furthermore, the circuit modification for recirculation of dialysate (to prevent loss of amino acids and other important elements in the dialysate) made the overall set-up less simple than it initially seemed. Interestingly, Nolte et al speculated that such a system might allow, in a 3-kg newborn, a clearance of 36 mL/min of CO2 (almost meeting the overall production) and that it might be achieved with a blood flow rate of 20 mL/kg/min. More recently, because of the growing interest in these techniques, Russ et al proposed a simplified, RRT-like method to remove CO2. Again, this was applied only to an experimental model, high volume hemofiltration (HVHF) (approximately 6 L/h), added by a predilutional THAM infusion at 8 mmol/kg/h, was shown to be highly effective in CO2 removal. It must be said that HVHF application is cumbersome and may be hampered by several side effects (ie, hypophosphatemia and a requirement of high anticoagulation doses or premature clotting). Furthermore, HVHF requires large vascular accesses, high blood flow rates (up to 400 mL/min), and technical expertise. Russ et al also described negative rheologic effects on the hemofilter secondary to profound acidosis. A dedicated ECCO2R system using a CO2 exchanging membrane now appears more technically feasible at the bedside using hemodialysis-adapted methods.
The modern era

Interestingly, paralleling the development of modern venovenous (VV) renal replacement from pioneering arterovenous (AV) hemofiltration, ECCO₂R has been performed through AV cannulation without the need for a pumping system and without the risk of an air embolism. Clearly, the blood flow rate in such a system and overall ECCO₂R efficiency is dependent on cannula diameter and patient AV pressure gradient, which may be reduced significantly in case of hemodynamic instability.³² Today, 14Fr to 18Fr venous double cannulas are used more commonly in a pumped system equipped with a membrane (gas exchanger) that allows the elimination of CO₂ through an oxygenator membrane at a rate of 300 to 500 mL/min.²⁵ Blood flow in ECCO₂R must be higher than that for RRT, but much lower than in extracorporeal membrane oxygenation (ECMO) systems because blood oxygenation is achieved only with blood flow rates greater than 3 to 5 L/min.⁴¹ A list of the commercially available devices with technical features is summarized in Table 1.

Today, novel ECCO₂R systems have been developed and the interest in this technique has increased exponentially. ECCO₂R generally is applied in two clinical conditions: for chronic obstructive pulmonary disease patients with hypercapnic respiratory failure who fail noninvasive ventilation,³⁴,³⁵ and ARDS patients undergoing PV with secondary hypercapnia.³⁶ The first field of application was analyzed recently by Sklar et al³⁷ in a systematic review evaluating the efficacy and safety of ECCO₂R in 87 patients with hypercapnic respiratory failure. Although caution is mandatory because only relatively low-quality studies (cases series, case reports, and two studies with historical controls) were included in the analysis, the majority of patients either were weaned successfully from MV or sustained on noninvasive ventilation, avoiding intubation. The reported complications mainly were bleeding episodes related to anticoagulation (8 severe and 13 minor events). Two major adverse events were associated with ECCO₂R: one retroperitoneal bleeding event occurred after femoral cannulation, and in one case intubation was necessary for hemodynamic instability. Thrombotic complications were reported in nine patients: membrane clotting leading to device failure may cause a rapid increase of CO₂, resulting in a life-threatening condition: intubation was necessary for filter clotting in 2 of 25 patients in one case series.²²

Efficacy, complication rates, and utility of ECCO₂R devices in patients with ARDS were addressed by Fitzgerald et al³⁸ in another systematic review. Fourteen studies with 495 patients (2 RCTs and 12 observational studies) were included for the analysis. VV ECCO₂R was used in seven studies, and AV configuration was used in the others. As far as the feasibility and efficacy of ECCO₂R were concerned, as an adjuvant system for PV in ARDS, final results were positive because CO₂ removal was quantitatively possible in almost all of the studies. On the other side, mortality was not improved by the application of this technique: however, a post hoc analysis of data from the most recent randomized controlled trials showed an improvement in ventilator-free days in more severe ARDS cases. Similar to the previously described review of chronic obstructive pulmonary disease, major weaknesses of this review were a general paucity of high-quality data and significant variation in both practice and technology used. Interestingly, the investigators observed that the complication rate seemed to decrease with improved familiarity of this technology. In addition, two of the included studies, one performed with VV³⁶ and one with AV devices,³⁹ showed that ECCO₂R was associated with lower sedation needs, a condition that previously has been associated with shorter ventilation time, shorter ICU and hospital stays, and a lower mortality rate.⁴⁰ More recently, Grasso et al,⁴¹ in an experimental model of ARDS, showed that the use of ECCO₂R (Abylcap; Bellco, Mirandola, Italy) running at 400 mL/min, permitted a reduction in the respiratory rate from 30.5 (3.8 SD) to 14.2 (3.5 SD) (P < .01) breaths/min, and minute ventilation from 10.4 (1.6 SD) to 4.9 (1.7 SD) L/min (P < .01) while maintaining the same PaCO₂ concentrations equivalent to the control group (high respiratory rate/minute volume). This was achieved because the ECCO₂R removed 38.9% (6.1 SD), which is equivalent to 79.9 (18.4 SD) mL/min of CO₂ production. In addition, as a clear demonstration of protective effects against biaura, during the lower respiratory rate conditions, IL-6, IL-8, and TNF-α concentrations were significantly lower in plasma, and IL-6 and TNF-α concentrations also were lower in the bronchoalveolar lavage.

INTEGRATION OF ECCO₂R AND CONTINUOUS RENAL REPLACEMENT THERAPY

Lung-renal support with extracorporeal systems in modern intensive care is not a novelty: patients undergoing ECMO frequently receive continuous RRT for kidney failure,⁴²,⁴³ but the ECCO₂R (low-flow) and the continuous renal replacement therapy (CRRT) system in patients with MOF may be integrated into a specific lung-renal support system (Fig. 1). Preliminary attempts to realize such a combination started approximately 25 years ago and were characterized by the replacement of the hemofilter with a gas exchanger. In 1992, Young et al⁴⁴ applied a CO₂ removal device (Capiox 350; Terumo Corporation, Tokyo, Japan) to a standard hemofiltration tubing set (Gambro...
Dialysatoren GmbH, Hechingen, Germany), in place of the hemofilter in an experimental setting that involved nine sheep. The pressure gradient was entrusted to an AV configuration (femoral–femoral) sustained by a pump (AK10; Gambro) that artificially pushed the blood up to 1,000 mL/min. The experimental study showed that a blood flow rate ranging from 470 to 600 mL/min, and 10 L/min of fresh dry oxygen, guaranteed satisfactory CO2 elimination (130-189 mL/min). Two main findings of this revolutionary study should be underlined: first, a lower blood flow rate than that considered in the past (1.3-1.5 L/min) was sufficient for extracorporeal CO2 clearance; and, second, CO2 removal can be applied to a standard CRRT circuit.

These considerations opened the door to further research: more recently, to test the technical effectiveness of a modern (easy-to-use) standard pump-driven RRT circuit, Godet et al instrumented five adult female healthy pigs with a low-flow CO2 removal device (PrismaLung, Gambro Baxter, Rome, Italy, Hospal, Gambro Baxter, Rome, Italy) integrated on a CRRT platform (a device based on the Prismaflex system, Gambro Baxter, Rome, Italy). The decarboxylation filter was a polymethylpentene infant hollow fiber gas exchanger (Medos Hilite 800 LT; Medos Medizin-Technik AG, Stolberg, Germany) with a surface area of 0.32 m² designed for a maximum blood flow of 800 mL/min. The study design comprised a progressive increase in blood flow rates from 200 to 400 mL/min, and sweep gas flows from 2 to 50 L/min with an oxygen fraction from 21% to 100%. Blood was withdrawn by a dual-lumen 13 Fr venous catheter (Gamcat; Gambro Hospal, Ltd, Volketswil, Switzerland) placed into the right jugular vein from the superior vena cava, and re-injected into the right atrium through the distal lumen of the catheter. The gas

Table 1. CO2 Removal Systems Currently Available on the Market

<table>
<thead>
<tr>
<th>Device</th>
<th>Company</th>
<th>Characteristics</th>
<th>Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>iLA-Membrane Ventilator</td>
<td>Novalung, Heilbronn, Germany</td>
<td>Membrane ventilator for pumpless (AV configuration) extrapulmonary lung support Surface area of gas exchange membrane 1.3 m²</td>
<td><a href="http://www.novalung.com">www.novalung.com</a></td>
</tr>
<tr>
<td>Novalung iLA active</td>
<td>Novalung, Heilbronn, Germany</td>
<td>From ECCO2R to ECMO Small portable diagonal pump and operational console It may run at low- or high-flow rates (0.5 to &gt; 4.5 L/min), covering a wide range of respiratory support from CO2 clearance to complete oxygenation and ventilation support (depending on the gas exchanger installed)</td>
<td><a href="http://www.novalung.com">www.novalung.com</a></td>
</tr>
<tr>
<td>PALP</td>
<td>Maquet, Rastatt, Germany</td>
<td>Low-flow system based on Maquet's Cardiohelp console (portable heart–lung support system - ECMO)</td>
<td><a href="http://www.maquet.com">www.maquet.com</a></td>
</tr>
<tr>
<td>Hemolung</td>
<td>A-lung Technologies, Pittsburgh; USA</td>
<td>ECCO2R Small (0.67 m²) surface area Specifically designed for CO2 removal, generally recommended for COPD patients</td>
<td><a href="http://www.alung.com">www.alung.com</a></td>
</tr>
<tr>
<td>Decap</td>
<td>Hemotec, Salerno, Italy</td>
<td>ECCO2R Uses a membrane lung (0.3-1.35 m²) connected in series with a hemodialysis filter Flow rates &lt; 500 mL/min Useful for patients requiring both pulmonary and renal support</td>
<td><a href="http://www.hemotec.com">www.hemotec.com</a></td>
</tr>
<tr>
<td>Abylcap</td>
<td>Bellco, Mirandola, Italy</td>
<td>ECCO2R Membrane surface area of 0.67 m², blood flow: 280-350 mL/min, phosphorylcholine coated</td>
<td><a href="http://www.bellco.net">www.bellco.net</a></td>
</tr>
<tr>
<td>PrismaLung</td>
<td>MedosMedizintechnik AG, Gambro, Hechingen, Germany</td>
<td>ECCO2R - CRRT The gas exchanger (0.32 m², heparin-coated, maximal blood flow rate: 450 mL/min) can be used in the presence or absence of the hemodialyzer</td>
<td><a href="http://www.gambro.com">www.gambro.com</a></td>
</tr>
<tr>
<td>Aferetica</td>
<td>Aferetica. Purification Therapy, Mirandola, Italy</td>
<td>ECCO2R - CRRT Blood flows 30-450 mL/min Infusion fluid in postdilution: after the HF and before the ECCO2R The kit allows performing the CO2 removal treatment for 5 days</td>
<td><a href="http://www.aferetica.com">www.aferetica.com</a></td>
</tr>
</tbody>
</table>

Abbreviations: COPD, chronic obstructive pulmonary disease; CPFA, coupled plasma filtration adsorption; HF, hemofilter; PALP, pump-assisted lung protection.
exchange membrane was connected into the CRRT circuit, in place of the hemofilter. Anticoagulation was obtained with unfractioned heparin targeted to an activated partial thromboplastin time (aPTT) of 150 to 180 seconds. Gas analysis before and after the gas exchanger showed a significant reduction of $\text{PCO}_2$ (-40.2 [13.0 SD] mm Hg; relative decrease, 46%; $P < .001$) and a 0.24 (0.06) increase of pH (7.21 before and 7.46 after filter; $P < .001$). The in vivo decrease in $\text{PaCO}_2$ was from 81.2 to 70.0 mm Hg ($P < .001$), corresponding to a mean decrease of 14%. The corresponding increase in pH was from 7.17 to 7.22.

As expected, the higher the blood flow and sweep gas, the higher the efficiency, and no significant changes in arterial blood oxygenation were observed regardless of oxygen concentration. The most significant aspect of the study by Godet et al is that it showed the feasibility of a respiratory support performed with a standard CRRT platform, opening to future applications for patients needing CO2 removal in centers where doctors are familiar with CRRT systems.

Figure 1. Schematic representation of an ECCO2R–CRRT system. The order of gas exchanger and hemofilter can be inverted depending on the manufacturer. CRRT can be performed with any modality: in this scheme hemofiltration is shown. In particular, predilution (pre-dil) hemofiltration can be administered before the membrane lung to reduce blood viscosity, coagulation factor concentration, and improve circuit patency. Circles represent system pumps and hexagons represent the required pressure sensors. Rep, replacement fluid pump; UF, ultrafiltration pump.
the gas exchanger was changed for clotting. The lung-assisting renal replacement system reduced the average systemic PacO₂ by 17.3 mm Hg (28.1%), and the pH increased by 0.12 in the first 4 hours. As expected, no change occurred in the patients’ PaO₂. In addition, a significant decrease in norepinephrine support was observed in all cases: in general, hemodynamic stability correlated with pH correction by enhanced CO₂ clearance.

In 2014, Quintard et al., 16 in 16 patients mechanically ventilated with respiratory acidosis and AKI requiring ongoing CRRT (continuous VV hemodialysis; Multi-filtrate, Fresenius Medical Care Italia, Palazzo Pignano, Italy), applied a gas exchanger (0.65-m² membrane surface, heparin-coated polypropylene) originally designed for pediatric ECMO (Hilite 2400 LT, Medos) in a serial manner upstream of the hemofilter. CRRT settings were left unchanged except for blood flow, which was increased to 400 mL/min, anticoagulation was maintained with unfractionated heparin (aPTT target, 45-50 s), and fresh gas flow for CO₂ washout was set at 10 L/min. Instead of a single 13.5-Fr/15-cm (jugular) or a 13.5-Fr/24-cm (femoral) double-lumen catheter, usually used for standard CRRT, a 16-Fr/27-cm femoral catheter (HemoSplit XK; Bard Access Systems, Inc, Salt Lake City, UT) was used or, alternatively, double cannulation was performed with two 13.5-Fr single-lumen catheters (or two double lumens, adapting them with a Y-shaped luer-lock connector). At the time ECCO₂R was started, all patients already were undergoing CRRT. The system significantly reduced the PacO₂ (-31% at 6 hours and -39% at 12 hours) and increased arterial pH (+0.16 at 6 hours and +0.23 at 12 hours). Again, no effect on oxygenation was observed and no complication was reported. The system was managed easily by the staff without adjunctive difficulties with respect to a standard CRRT. Interestingly, because the CRRT circuit is limited to a 72-hour use, and the Hilite 2400 LT membrane commonly is used for up to 21 days, the membrane was disconnected, rinsed with saline in a sterile manner, and reconnected to the new circuit every 72 hours (mean treatment, 6 days).

CONCLUSIONS

In modern intensive care medicine, lungs and kidneys represent the most often affected organs in patients with MOF due to shock, trauma, or sepsis, resulting in a high mortality rate. These patients often need lung support for respiratory failure and renal replacement for severe AKI. Moreover, besides a common cause, which may lead to multiorgan failure involving lung and kidneys (eg, sepsis), there is a specific (negative) interaction and cross-talk, likely identifying a lung-renal syndrome. Lung support with MV may worsen kidney function further, and reducing pulmonary mechanical stress has been shown to possibly limit the negative effects on distal organs. PV with low tidal volumes and airway pressures has become the standard of care in modern intensive care and now is considered a routine (highly recommended) practice. Pioneering extracorporeal monitors for dialysis were introduced into the ICU more than 20 years ago, 48 and ECCO₂R systems currently are undergoing quick and significant technical development and their application to critically ill patients is becoming safe and feasible. The real novelty in the treatment of respiratory-renal insufficiency is the possibility of simultaneously supporting lungs and kidneys by ECCO₂R and CRRT implementation into a unique platform. A system including CRRT and ECCO₂R may have significant advantages, especially in nonspecialized centers, which are experienced in CRRT but do not have dedicated surgical/perfusion staff for invasive full ECMO-CRRT support. To date, experimental and clinical experiences still are lacking and additional, larger, and controlled studies certainly are needed to assess the impact of combined ECCO₂R-CRRT systems in critically ill patients: the era of multiple organ support has just begun.

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