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Extracorporeal Co_2 Removal for Chronic Obstructive Pulmonary Disease: Too Risky or Ready for a Trial?*

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In this issue of *Critical Care Medicine*, using an interesting case-control study design, Del Sorbo et al (1) have tried to assess the efficacy of extracorporeal Co_2 removal ($ECCo_2R$) in hypercapnic patients at risk of noninvasive ventilation (NIV) failure. They enrolled patients treated with NIV for acute hypercapnic respiratory failure because of exacerbation of COPD in two Italian ICUs, and also managed with $ECCo_2R$ because they were considered as high risk of NIV failure, including a pH less than 7.30. During $ECCo_2R$, continuous infusion of heparin was titrated to maintain full anticoagulation (activated partial thromboplastin time ratio to 1.5). These patients were matched with similar patients from two previous cohorts treated with NIV only and reaching the same risk criteria for failure. Of importance, among the 89 patients who clinically reached the criteria for $ECCo_2R$ implementation (risk of NIV failure), only 25 were enrolled whereas the remaining were not included for medical reasons in 10 cases (low blood pressure, contraindications to anticoagulation, and obesity), contraindication to continuation of active treatment in 13, and failure to obtain consent in 41.

The topic is clinically relevant, the approach is innovative and takes profit of the major technical improvements offered by industry in this field. The general principle is that $ECCo_2R$ could be used technically like a simple continuous venovenous hemofiltration circuit but which primary goal would be to eliminate Co_2 from the blood. The major difference with the technique described as venovenous extracorporeal membrane oxygenation (ECMO) is that much lower blood flows are needed to remove Co_2, around 300 to 1,500 mL/min (range between 177 and 333 mL/min in the study of Del Sorbo et al [1]) when compared with 3–5 L/min with ECMO. The major advantage of the low flow is that relatively small vascular cannulas can be used for this amount of blood flow (14F in this study) although usually slightly larger than for continuous venovenous hemofiltration. The disadvantage of a low flow passing through a membrane is that the risk of clotting is very high, and full anticoagulation is required.

The results of the authors favor the use of $ECCo_2R$ in this specific indication because intubation rate in patients receiving NIV-plus-$ECCo_2R$ was 12% when compared with 33% in those kept only with NIV, but the difference was not statistically different. Another analysis suggested that the risk of intubation was significantly reduced by $ECCo_2R$. Of note, the criteria for a high risk of NIV failure were performing only modestly because no more than 30% of patients required

*See also p. 120.

Key Words: chronic obstructive pulmonary disease; hemorrhagic complications; membrane oxygenator; noninvasive ventilation

Dr. Brochard consulted for Covidien (research on proportional assist ventilation [PAV]). His institution received grant support from Covidien (research on PAV), General Electric (research on functional residual capacity), and Maquet (research on neurally adjusted ventilatory assist). His institution has patents with and received support for the development of educational presentations from General Electric. Dr. Beloncle received grant support from the University Hospital of Angers.

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intubation in the NIV-only group. The results, therefore, indicate that a randomized trial is needed at this stage to assess the clinical benefit of this technique in this indication.

One of the major points raised by the study of Del Sorbo et al (1), however, is the high complication rate associated with the use of $ECCO_2R$. $ECCO_2R$-related complications were observed in almost half of the patients. A main source of complications stems from anticoagulation. Despite the exclusion of patients with high hemorrhagic risk and carefully titrated anticoagulation during extracorporeal circulation, significant bleeding developed in three patients (15%) in the study by Del Sorbo et al (1). Similar hemorrhagic complication rates were found in some recently published studies using comparable $ECCO_2R$ devices (2, 3). In a randomized control trial comparing a ventilation strategy with a very low tidal volume combined with $ECCO_2R$ versus a conventional protective ventilation in 79 patients with severe ARDS, the need for RBCs transfusion was significantly higher in the $ECCO_2R$ group than in the control group (4). Other studies using $ECCO_2R$ reported low (or even nonexistent) bleeding risk (5–8). Aside from the differences in the devices, patient populations, and protocols used, the small sizes of these studies may, in part, explain the heterogeneity of the results.

Even with low hemorrhagic risk, however, one should not minimize the potential severity of these complications, especially when considering the adjunctive nature of this technique. In a series including 21 patients, Burki et al (3) reported one death caused by a retroperitoneal bleed following catheterization. In a larger cohort of 90 patients, Bein et al (7) reported one intracerebral hemorrhage and one hemorrhagic shock.

Paradoxically, many of the complications were coming from insufficient anticoagulation. Unlike renal replacement therapy, where circuit coagulation is mainly associated with blood loss and does not usually lead to a life-threatening situation, clotting during $ECCO_2R$ may lead to a rapid increase in Co_2 load in the body, resulting in severe respiratory acidosis necessitating intubation if the patient is not intubated and not able to adapt to this huge change in ventilatory needs. In the study by Del Sorbo et al (1), 6 (30%) patients treated with $ECCO_2R$ experienced clotting in the extracorporeal circuit leading to intubation in two of these cases. Consequently, a decrease in the anticoagulation level seems unlikely to decrease the global rate of complications and could even worsen morbidity in this study population.

Finally, there are risks related to the need of a relatively large-diameter catheter, including arterial puncture, venous thrombosis, aneurysm, hematoma formation or infection, and even pneumothorax and air embolism. The size of this cohort does not allow us to draw definitive conclusions and a learning curve may also exist. During renal replacement therapy, the catheters are usually smaller: rare but potentially severe complications are expected (9, 10).

These observations raise several questions. First, are all the different Co_2 removal devices/membranes equivalent in terms of hemorrhagic risk and need for anticoagulation? In particular, the difference in complication rates between pumpless devices creating an arteriovenous shunt (2, 4, 6, 7) and devices using venous dual lumen catheter and a pump driving blood flow (1, 3, 5, 8) needs to be assessed. Second, would more restrictive patient selection and a better individualized anticoagulation protocol allow to reduce this complication rate?

As acknowledged by the authors, these complications contrast with major potential therapeutic effect. This may justify the implementation of a randomized controlled trial. We need to be sure, however, that we have minimized the risk associated with this technique. Additional clinical and physiological studies carefully looking at coagulation may help in better understanding and controlling this aspect.

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Extracorporeal Co_2 Removal in Hypercapnic Patients At Risk of Noninvasive Ventilation Failure: A Matched Cohort Study With Historical Control*

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Objectives: To assess efficacy and safety of noninvasive ventilation-plus-extracorporeal Co_2 removal in comparison to noninvasive ventilation-only to prevent endotracheal intubation patients with acute hypercapnic respiratory failure at risk of failing noninvasive ventilation.

Design: Matched cohort study with historical control.

Setting: Two academic Italian ICUs.

Patients: Patients treated with noninvasive ventilation for acute hypercapnic respiratory failure due to exacerbation of chronic obstructive pulmonary disease (May 2011 to November 2013).

Interventions: Extracorporeal Co_2 removal was added to noninvasive ventilation when noninvasive ventilation was at risk of failure (arterial pH ≤ 7.30 with arterial Pco_2 > 20% of baseline, and respiratory rate ≥ 30 breaths/min or use of accessory muscles/paradoxical abdominal movements). The noninvasive ventilation-only group was created applying the genetic matching technique (GenMatch) on a dataset including patients enrolled in two previous studies. Exclusion criteria for both groups were mean arterial pressure less than 60 mm Hg, contraindications to anticoagulation, body weight greater than 120 kg, contraindication to continuation of active treatment, and failure to obtain consent.

Measurements and Main Results: Primary endpoint was the cumulative prevalence of endotracheal intubation. Twenty-five patients were included in the noninvasive ventilation-plus-extracorporeal Co_2 removal group. The GenMatch identified 21 patients for the noninvasive ventilation-only group. Risk of being intubated was three times higher in patients treated with noninvasive ventilation-only than in patients treated with noninvasive ventilation-plus-extracorporeal Co_2 removal (hazard ratio, 0.27; 95% CI, 0.07–0.98; $p = 0.047$). Intubation rate in noninvasive ventilation-plus-extracorporeal Co_2 removal was 12% (95% CI, 2.5–31.2) and in noninvasive ventilation-only was 33% (95% CI, 14.6–57.0), but the difference was not statistically different ($p = 0.1495$). Thirteen patients (52%) experienced adverse events related to extracorporeal Co_2 removal. Bleeding episodes were observed in three patients, and one patient experienced vein perforation. Malfunctioning of the system caused all other adverse events.

Conclusions: These data provide the rationale for future randomized clinical trials that are required to validate extracorporeal Co_2 removal in patients with hypercapnic respiratory failure and respiratory acidosis nonresponsive to noninvasive ventilation. (*Crit Care Med* 2015; 43:120–127)

***See also p. 245.**

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Key Words: acute hypercapnic respiratory failure; chronic obstructive pulmonary disease; extracorporeal Co_2 removal; mechanical ventilation; noninvasive ventilation; respiratory acidosis

Noninvasive ventilation (NIV) represents the standard of care for patients with exacerbation of chronic obstructive pulmonary disease (COPD) who need admission to the ICU for management of acute hypercapnic respiratory failure and severe respiratory acidosis (1). NIV fails in almost 40% of the most severe forms of acute hypercapnic respiratory failure, and patients must undergo endotracheal intubation and invasive ventilation to restore adequate gas exchange (2–4). Patients requiring transition from NIV to invasive ventilation have greater odds of death compared with patients successfully treated with NIV alone (5).

The clinical efficacy of NIV is based on its ability to wash out the excessive Co_2 by increasing alveolar ventilation (6). Extracorporeal circuits designed to remove Co_2 (extracorporeal Co_2 removal [$ECCO_2R$]) have been used in patients with acute hypercapnic respiratory failure (7–20) since $ECCO_2R$ should enhance the efficacy of NIV to remove Co_2 (8, 10, 16, 20) and avoid the worsening of respiratory acidosis (4, 21). Although available studies are limited to description of single cases (11–15) or to case series (7–10) and comparison between "NIV-plus-$ECCO_2R$" and "NIV-only" in patients at risk of NIV failure is not available, several $ECCO_2R$ devices have been developed and proposed for patients with COPD (Maquet PULP: Available at: http://www.maquet.com; Novalung iLA active: Available at: http://www.novalung.com; Alung, Hemolung®RAS: Available at: http://www.alung.com; Hemodec, Decap: Available at: http://www.hemodec.com; Bellco, Abylcap: Available at: http://www.bellco.net).

The present study estimates the efficacy and safety of $ECCO_2R$ in association to NIV to reduce need of endotracheal intubation in hypercapnic patients at risk of NIV failure. Since need of intubation for NIV failure progressively decreased (1), patients included in the present study may not represent hypercapnic patients commonly treated with NIV, and the proposed indication for $ECCO_2R$ may be a niche.

METHODS

We enrolled patients older than 18 and younger than 90 years treated with NIV for acute hypercapnic respiratory failure due to exacerbation of COPD in two Italian ICUs (May 2011 to November 2013). Review boards approved the protocol, and patients provided written consent.

NIV-Plus-$ECCO_2R$

Patients with COPD exacerbation and treated with NIV for acute hypercapnic respiratory failure were included. $ECCO_2R$ was added to NIV in patients who were considered as being "at risk of failure of NIV" when, after at least 2 hours of continuous application of NIV, arterial pH was less than or equal to 7.30 with a $Paco_2$ greater than 20% of the baseline value and one of the following was observed: respiratory rate greater than or equal to 30 breaths/min and use of accessory muscles or paradoxical abdominal movements (4). Exclusion criteria were as follows: mean arterial pressure less than 60 mm Hg despite infusion of fluids and vasoactive drugs; contraindications to anticoagulation (i.e., any of the following: platelet count < 30,000/mm^3; prothrombin time-international normalized ratio > 1.5); stroke or severe head trauma or intracranial arteriovenous malformation, or cerebral aneurysm, or CNS mass lesion within the previous 3 months; epidural catheter in place or expected to be positioned during the study; history of congenital bleeding diatheses; gastrointestinal bleeding within the 6 weeks prior to study entry; esophageal varices, chronic jaundice, cirrhosis, or chronic ascites; trauma; body weight greater than 120 kg; contraindication to continuation of active treatment; and failure to obtain consent. The institutional ethics committee approved collection and report of data at ICU admission and hospital release of patients that did not provide consent to treatment with $ECCO_2R$ use.

An $ECCO_2R$ device based on a modified continuous venovenous hemofiltration system (Decap Smart, Hemodec, Salerno, Italy) was used (22). Blood flow is driven by a roller nonocclusive pump (0–450 mL/min) through a polypropylene oxygenator (Euroset, Medolla [Modena], Italy; priming volume, 100 mL; contact surface area, 1.35 m^2; maximum blood flow rate, 7 L/min) that is connected to a fresh gas flow source delivering 100% oxygen at a constant rate of 8 L/min. Exiting the oxygenator, blood is driven to a hemofilter (Medica D250, Medolla, Italy). The resulting plasmatic water is recirculated through the membrane lung by a peristaltic pump (0–155 mL/min). A starting dose of heparin (80 IU/kg bolus and 18 IU/kg/hr infusion) was delivered by using a syringe pump included in the system. Continuous infusion of heparin was hence titrated to maintain the activated partial thromboplastin time (aPTT) ratio to approximately 1.5 and checked approximately every 2–3 hours. The femoral vein was accessed via a double-lumen catheter (14F; Joline GmbH & Co. KG, Hechingen, Germany) (22).

$ECCO_2R$ was interrupted and patients reverted to the "NIV-only" treatment when all of the following were achieved for at least 12 hours: respiratory rate less than 25 breaths/min; pH greater than 7.35; $Paco_2$ less than 20% of the baseline value; and absence of use of the accessory muscles or paradoxical abdominal movements.

NIV-Only

A dataset for matched cohort analysis was created using patients treated with "NIV-only" for COPD and acute hypercapnic respiratory failure enrolled in two previous studies performed in the same institutions where the present investigation was carried out (23, 24). Patients were considered for matching if "at risk of failure on NIV" using the same criteria as for the "NIV-plus-$ECCO_2R$" group (4). Exclusion criteria were the same as for the "NIV-plus-$ECCO_2R$" group.

Study Endpoints

Primary endpoint was the cumulative prevalence of endotracheal intubation during the 28 days after ICU admission.

Decision to intubate was taken by the attending clinicians not involved in the study when two of the following occurred for at least 2 hours: respiratory frequency greater than 35 breaths/min; arterial pH less than 7.25; $Paco_2$ greater than 60 mm Hg; Pao_2 less than 60 mm Hg with an Fio_2 greater than 60%; respiratory arrest; and signs of patient distress with accessory muscle recruitment and paradoxical abdominal or thoracic motion. In addition, intubation was performed when any of the following was observed (6): hemodynamic instability defined as 80–90 mm Hg increase or a 30–40 mm Hg decrease in systolic blood pressure relative to the baseline value or need for inotropic drugs to maintain systolic blood pressure higher than 85 mm Hg or electrocardiogram evidence of ischemia or significant ventricular arrhythmias; need for sedation for major agitation; decreased alertness defined as a Glasgow Coma Score less than 9; and cardiac arrest (6, 23–26). Patients were followed up until hospital discharge or death. Secondary endpoints were in-hospital mortality and ICU and hospital length of stay.

Potential adverse events related to $ECCO_2R$ were recorded and classified as mechanical (membrane lung failure, clots/air in the circuit, pump malfunction, tubing rupture, catheter displacement, and system leaks) and patient-related (vein perforation at cannula insertion, significant bleeding [i.e., any bleeding event that required the administration of 1 U of packed red cells], hemodynamic instability [i.e., 80–90 mm Hg increase or 30–40 mm Hg decrease in systolic blood pressure relative to the baseline value or need for inotropic drugs for at least 2 hr to maintain systolic blood pressure higher than 85 mm Hg or electrocardiogram evidence of ischemia or significant ventricular arrhythmias], ischemic/gangrenous bowel, pneumothorax, renal complications [i.e., occurrence after initiation of Co_2 removal of creatinine > 1.5 mg/dL], infectious complications [i.e., occurrence after initiation of Co_2 removal of culture-proven new infection], metabolic complications [i.e., occurrence after initiation of Co_2 removal of glucose of at least 240 mg/dL or hyperbilirubinemia], thromboembolic complications [i.e., occurrence after initiation of deep venous thrombosis or pulmonary embolus], and neurologic complications [i.e., occurrence after initiation of Co_2 removal of cerebral infarction, or clinical seizure, or cerebral hemorrhage or cerebral edema]) (22).

Statistical Analysis

The propensity score of receiving $ECCO_2R$, that is, the subject's probability of receiving the study treatment conditionally to a number of observed covariates presumed to be associated with the decision to use $ECCO_2R$ was assessed using a multivariable logistic regression analysis with $ECCO_2R$ treatment as the dependent variable. The a priori selected variables (4, 21) were age; forced expiratory volume in the 1st second (FEV_1); Charlson comorbidity index (27); Simplified Acute Physiology Score (SAPS) II (28); and value of pH before institution of mechanical ventilation. Except for FEV_1 (taken from the most recent pulmonary function test), all variables were obtained at ICU admission.

The genetic matching method without replacement (GenMatch) was used to match patients treated with "NIV-plus-$ECCO_2R$" and "NIV-only" (29, 30). GenMatch is a multivariate matching technique that aims to make the distribution of baseline characteristics between "control" and "intervention" as similar as possible combining propensity score matching with multivariate matching. The automated search algorithm makes the multivariate distribution of covariates in the matched "control" and "intervention" groups as similar as possible by estimating the relative weight of the propensity score and of the selected individual; iteratively checking the balance and directing the search toward matches that optimize balance; selecting those weights that give the best covariate balance in the matched samples (29, 30). The balance statistics was performed using the Wilcoxon-Mann-Whitney test (29, 30).

To ascertain whether inclusion criteria influenced the base-case findings, all analyses were repeated eliminating from both groups patients with severe neurological impairment (Kelly score ≥ 3) and patients with severe hypoxemia ($Pao_2/Fio_2 < 150$) since both are associated to high risk of failure of NIV (4, 21).

Data are presented as mean (SD) or median (interquartile range). Comparison between and within groups was made using the Wilcoxon-Mann-Whitney test for continuous variables and the chi-square or the Fisher exact test for categorical variables. Results are reported as hazard ratio (HR) with 95% CIs. Cumulative prevalence of endotracheal intubation during the 28 days immediately after ICU admission was assessed considering death as a competing event using the method of Gooley. Adjusted HR and 95% CI were estimated using the Fine and Grey model.

All statistical tests were two-sided and p values of 0.05 or less were considered statistically significant and were conducted using the following software packages: Stata (StataCorp, College Station, TX), R (R Foundation for Statistical Computing, http://www.r-project.org/), and SAS (SAS Institute, Cary, NC).

RESULTS

Two hundred patients with acute hypercapnic respiratory failure due to exacerbation of COPD were admitted for treatment with NIV. Of the 89 patients that matched criteria for being at risk of intubation for NIV failure, 25 patients were treated with "NIV-plus-$ECCO_2R$." The remaining 64 patients were not included for the following reasons: mean arterial pressure less than 60 mm Hg despite infusion of fluids and vasoactive drugs ($n = 2$), contraindications to anticoagulation ($n = 4$), body weight greater than 120 kg ($n = 4$), contraindication to continuation of active treatment ($n = 13$), and failure to obtain consent ($n = 41$). Of the 198 COPD patients with acute hypercapnic respiratory failure treated with "NIV-only" and previously enrolled (23, 24), 105 patients met inclusion criteria for being at risk of intubation for NIV failure and 84 patients were eligible for GenMatch analysis. The remaining 21 patients were not included for the following reasons: mean arterial pressure less than 60 mm Hg despite infusion of fluids and vasoactive drugs ($n = 6$), contraindications to anticoagulation ($n = 4$), body weight greater than 120 kg ($n = 3$), and contraindication to continuation of active treatment ($n = 8$). The GenMatch procedure identified 21 patients from the "NIV-only" group to be compared with the 25 patients of the "NIV-plus-$ECCO_2R$" group (**Fig. 1**).

Before matching, age and SAPS II score were higher and Charlson comorbidity index was lower in "NIV-only" than in "NIV-plus-ECCO$_2$R" ($p = 0.0482$, 0.0025, and 0.0112, respectively). After matching, there was no difference in baseline characteristics between "NIV-plus-ECCO$_2$R" and "NIV-only" groups (**Table 1**). Characteristics of patients at risk of NIV failure but not included in the study protocol (64 patients for the "NIV-plus-ECCO$_2$R" group and 21 patients for the "NIV-only" group) did not differ from those included in the final analysis (data presented in the **online data supplement**, Supplemental Digital Content 1, http://links.lww.com/CCM/B63).

A significant reduction of $Paco_2$ from baseline ($p = 0.0037$) and an increase in arterial pH ($p < 0.0001$) were observed after 1 hour of treatment only in patients treated with "NIV-plus-ECCO$_2$R" (**Table 2**). The reduction in respiratory rate after 1 hour of treatment was larger in "NIV-plus-ECCO$_2$R" than in "NIV-only" (31% ± 20% vs 11% ± 17% before and after, respectively; $p = 0.01$).

Figure 2 shows the cumulative prevalence of endotracheal intubation in "NIV-plus-ECCO$_2$R" and "NIV-only." Application of ECCO$_2$R during NIV decreased risk of intubation relative to "NIV-only" by 73% (HR, 0.27; 95% CI, 0.07–0.98; $p = 0.047$). Intubation rate in the "NIV-plus-ECCO$_2$R" group was 12% (three patients; 95% CI, 2.5–31.2), whereas in "NIV-only" was 33% (seven patients; 95% CI, 14.6–57.0; $p = 0.1495$). Analysis was repeated eliminating patients with severe hypoxemia ($Pao_2/Fio_2 < 150$) and patients with severe neurological impairment (Kelly score ≥ 3). In patients without severe hypoxemia, intubation was observed in two out of 22 patients (9%; 95% CI, 1.1–29.2) in "NIV-plus-ECCO$_2$R" and in seven out of 17 patients (41%; 95% CI, 18.4–67.0) in "NIV-only" ($p = 0.0262$). In patients without severe neurological impairment, intubation was observed in 1 out of 16 patients (6%; 95% CI, 0.2–30.2) in "NIV-plus-ECCO$_2$R" and in six out of 13 patients (46%; 95% CI, 19.2–74.9) in "NIV-only" ($p = 0.026$) (**Fig. 3**). Indications and timing of intubation are presented in the Online data supplement (Supplemental Digital Content 1, http://links.lww.com/CCM/B63).

Hospital mortality was significantly ($p < 0.05$) lower in "NIV-plus-ECCO$_2$R" than in "NIV-only" (8% [95% CI, 1.0–26.0] vs 33% [95% CI, 18.0–57.5], respectively) (**Table 3**).

Data of the "NIV-only" group before matching are presented in the online data supplement (Supplemental Digital Content 1, http://links.lww.com/CCM/B63).

Thirteen patients (52%) experienced adverse events related to ECCO$_2$R (**Table 4**). All endotracheal intubations observed were due to ECCO$_2$R-related adverse events. Patient 4 received invasive mechanical ventilation for severe hemodynamic instability consequent to retroperitoneal bleeding. In patients 14 and 19, clots in the circuit caused interruption of ECCO$_2$R with consequent severe respiratory acidosis that required endotracheal intubation.

The use of ECCO$_2$R ranged between 24 and 41 hours. Blood flow through the extracorporeal circuit ranged between 177

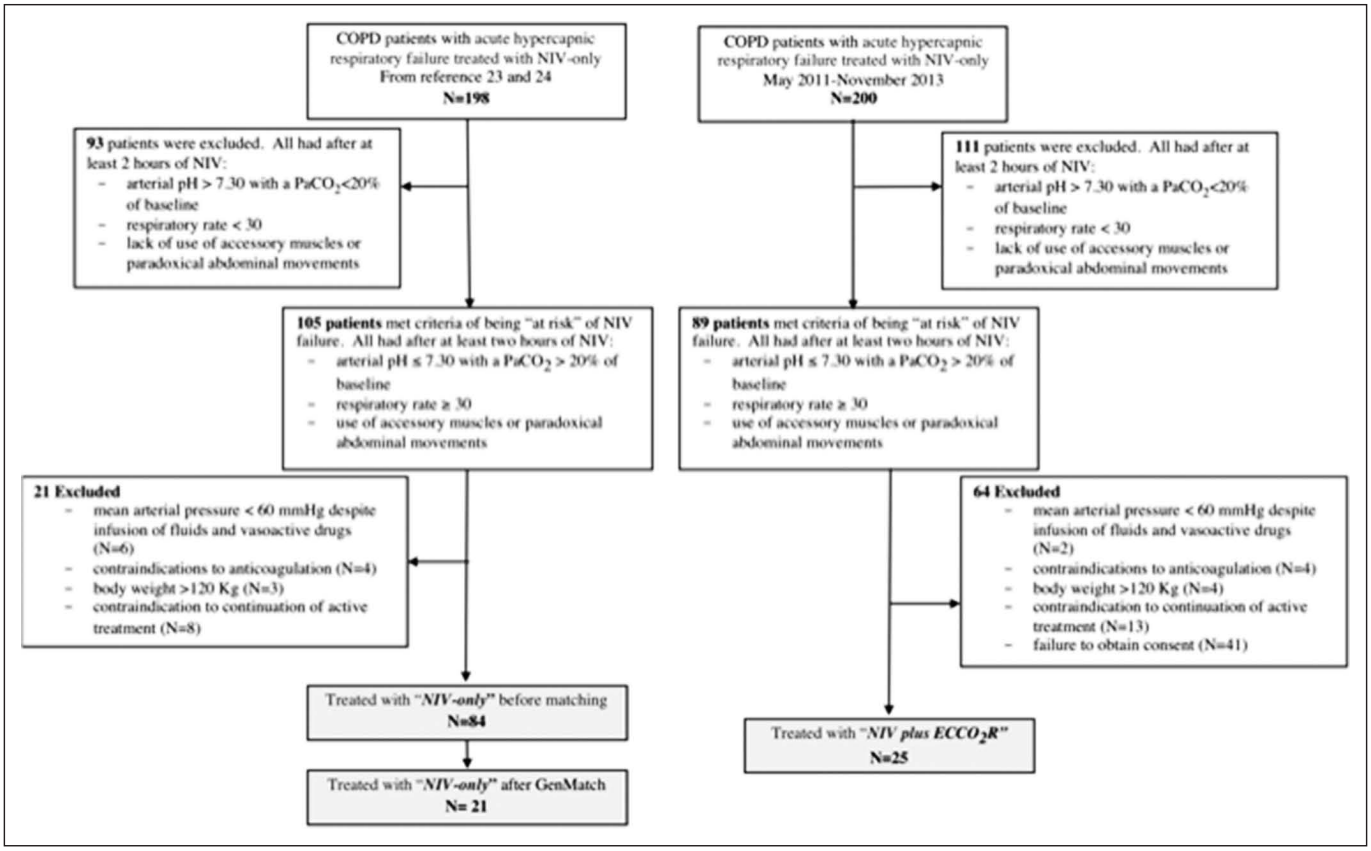

Figure 1. Patient's characteristics and selection criteria for inclusion in study analysis. COPD = chronic obstructive pulmonary disease, ECCO$_2$R = extracorporeal Co_2 removal, GenMatch = genetic matching, NIV = noninvasive ventilation.

TABLE 1. Characteristics of Noninvasive Ventilation-Plus-Extracorporeal Co_2 Removal and Noninvasive Ventilation-Only Treated Patients Before and After Matching

Study Variables	NIV-Plus-Extracorporeal Co_2 Removal[a]	NIV-Only			
		Before Matching[b]	*p*	After Genetic Matching[c]	*p*
Age, yr	70.7 (7.1)	74.2 (9.2)	0.0482	70.4 (9.8)	0.8778
Forced expiratory volume in the 1st second, L	30.80 (8.79)	26.88 (11.51)	0.0875	28.7 (11.4)	0.6374
Simplified Acute Physiology Score II[d]	36.52 (5.24)	44.42 (12.25)	0.0025	36.14 (6.05)	0.6364
Arterial pH before institution of NIV	7.26 (0.08)	7.25 (0.09)	0.7004	7.27 (0.07)	0.3938
Charlson comorbidity index[e]	6.08 (2.08)	4.86 (2.68)	0.0112	6.10 (2.36)	0.8590

NIV = noninvasive ventilation.

[a]There were 25 patients for the NIV-plus-extracorporeal Co_2 removal–treated group.

[b]There were 84 patients for the NIV-only–treated group.

[c]There were 21 patients for the NIV-only–treated group.

[d]An index of the severity of illness, higher values indicate greater severity (range, 0 and 163).

[e]The Charlson comorbidity index predicts the 10-year mortality for a patient who may have a range of comorbid conditions, such as heart disease or cancer (a total of 22 conditions). Each condition is assigned a score of 1, 2, 3, or 6, depending on the risk of dying associated with each one.

Data are mean (SD) or median and interquartile range. Comparisons between groups were made using the Wilcoxon-Mann-Whitney test.

TABLE 2. Respiratory Variables in Noninvasive Ventilation-Plus-Extracorporeal Co_2 Removal and Noninvasive Ventilation-Only

Study Variables	NIV-Plus-Extracorporeal Co_2 Removal ($n = 25$)	NIV-Only After Genetic Matching ($n = 21$)	*p*
$Paco_2$, mm Hg	$p = 0.0037$	$p = 0.7363$	
T_0	88.0 (67.0; 96.0)	82.0 (76.0; 89.0)	0.6067
T_1	63.0 (52.0; 84.0)	80.0 (66.0; 104.5)	0.0125
Arterial pH	$p < 0.0001$	$p = 0.4979$	
T_0	7.27 (7.25; 7.28)	7.28 (7.23; 7.30)	0.2423
T_1	7.34 (7.32; 7.39)	7.28 (7.17; 7.30)	0.0003
Respiratory rate, breaths/min	$p < 0.0001$	$p = 0.1268$	
T_0	32 (29, 35)	30 (28, 32)	0.2641
T_1	22 (18, 24)	27 (25, 31)	0.0002
Pao_2/Fio_2	$p = 0.9493$	$p = 0.0701$	
T_0	168 (133; 210)	176 (152; 233)	0.3648
T_1	178 (131; 203)	235 (212; 262)	0.0006

NIV = noninvasive ventilation, T_0 = time 0, time when criteria for "risk of NIV failure" were matched, T_1 = time 1, time 0 plus 1 hr.

Data are expressed as median (interquartile range). . Comparisons between and within groups are made using the Wilcoxon-Mann-Whitney test.

and 333 mL/min. The dose of heparin required to maintaining the aPTT ratio between 1.22 and 2.54 ranged between 10.3 and 17.3 IU/kg (**Table 5**).

DISCUSSION

Recent preliminary reports (7–20) have described the use of $ECCO_2R$ in patients with COPD fostering the concept that extracorporeal support in patients with hypercapnic respiratory failure may improve outcome (17, 19, 20) and sustaining the development of several $ECCO_2R$ devices that have been proposed for patients with COPD (Maquet PULP: Available at: http://www.maquet.com; Novalung iLA active: Available at: http://www.novalung.com; Alung, Hemolung®RAS: Available at: http://www.alung.com; Hemodec, Decap: Available at: http://www.hemodec.com; Bellco, Abylcap: Available at: http://www.bellco.net. Accessed February 24, 2014). Our

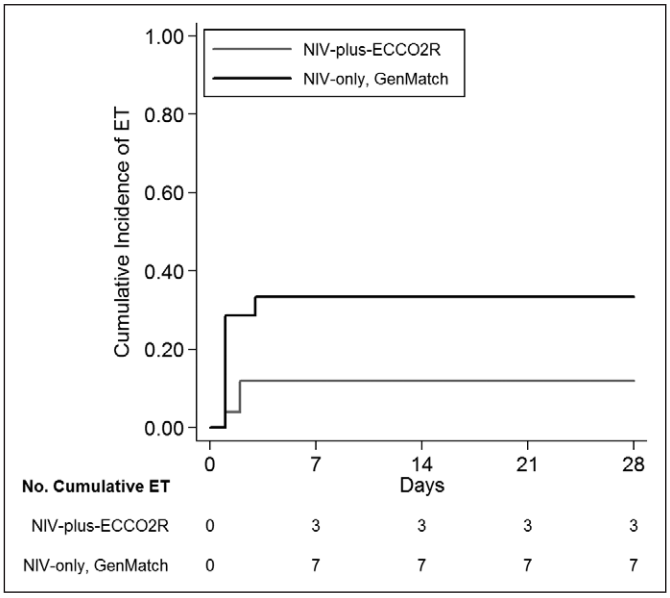

Figure 2. Cumulative prevalence curves of endotracheal intubation in "noninvasive ventilation (NIV)-plus-extracorporeal Co_2 removal ($ECCO_2R$)" versus "NIV-only." Before matching, the hazard ratio of intubation in the NIV-plus-$ECCO_2R$ versus NIV-only treated group was 0.32 (95% CI, 0.09–1.08; $p = 0.066$). After genetic matching (GenMatch), the hazard ratio was 0.27 (95% CI, 0.07–0.98; $p = 0.047$). ET = endotracheal intubation.

data show that hazard of being intubated was three times higher in patients treated with "NIV-only" than in patients treated with "NIV-plus-$ECCO_2R$." However, although intubation rate in "NIV-plus-$ECCO_2R$" was lower than "NIV-only," the difference was not statistically significant. These data, and the fact that $ECCO_2R$-related complications were observed in almost half of the patients, leave open to future randomized clinical trials the question whether patients with respiratory acidosis refractory to NIV should be intubated and take the risks associated with invasive mechanical ventilation, or should be connected to $ECCO_2R$ to avoid intubation, but run the risk of the potentially serious $ECCO_2R$-related complication.

Use of NIV improves outcome in patients with acute hypercapnic respiratory failure (21). Patients who fail NIV and need endotracheal intubation have a higher odds of death than patients who are successfully treated with NIV (5). In patients with pH less than 7.30, prevalence of NIV failure ranges between 26% (6) and 52% (3). In the present study, patients included in the "NIV-plus-$ECCO_2R$" and "NIV-only" groups were at high risk of failing NIV since they all had severe respiratory acidosis and high respiratory rate that did not improve with NIV (4). In the "NIV-only" group, intubation rate was 48%. This value is consistent with predictive models (4) and previous studies (2, 3). In the "NIV-plus-$ECCO_2R$" treated group, we observed a 73% risk reduction of intubation that could be attributed to the observed increase in arterial pH, decrease in $Paco_2$, and more enhanced reduction of respiratory rate (Table 2). In fact, failure of NIV is associated to no improvement of pH and respiratory rate with ventilatory support (4, 21).

The strength of this study lies in the homogeneity of the patients and the robustness of the matching method used. First, we included patients with a priori identified characteristics that are able to describe general conditions (age and comorbidities) and severity of the impairment of respiratory function (FEV_1) and acute critical illness (SAPS II) and are all associated to the risk of failing NIV (1). Furthermore, we excluded those patients in whom $ECCO_2R$ would have been hard to be implemented (mean arterial pressure < 60 mm Hg, body weight > 120 kg) or not recommended (risk of bleeding or contraindication to continuation of active treatment) (18). Furthermore, to ascertain whether inclusion criteria influenced the base-case findings, we validated our results adding severe hypoxemia (Pao_2/Fio_2 < 150) and severe neurological impairment (Kelly score ≥ 3) as alternative exclusion criteria (30). Second, to match "NIV-plus-$ECCO_2R$" with "NIV-only" we used the GenMatch technique, a multivariate matching method that combines propensity score matching with multivariate matching (29–31). GenMatch creates matched clusters of data using an automated evolutionary search algorithm that weights the propensity

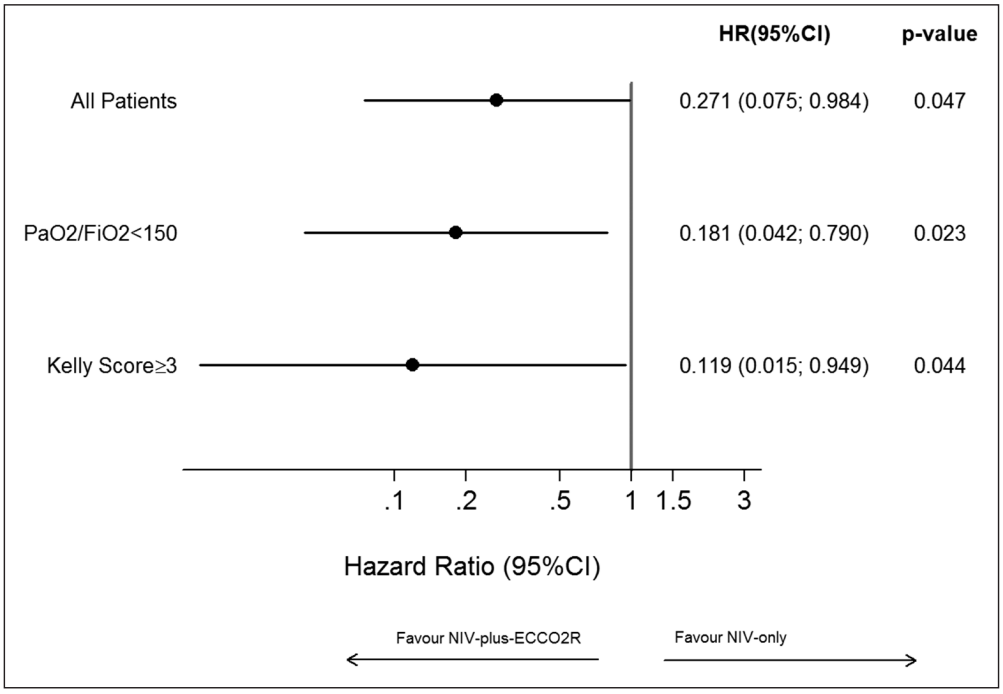

Figure 3. Stratified analysis for "noninvasive ventilation (NIV)-plus-extracorporeal Co_2 removal ($ECCO_2R$)" versus "NIV-only" before matching and after genetic matching. HR = hazard ratio.

TABLE 3. Study Secondary Endpoints

Study Variables	NIV-Plus-Extracorporeal Co_2 Removal ($n = 25$)	NIV-Only After Genetic Matching ($n = 21$)	p
Hospital mortality, *n* (%)	2 (8)	8 (35)	0.0347
ICU length of stay (d)	8 (7, 10)	12 (6, 15)	0.1943
Hospital length of stay (d)	24 (21, 28)	22 (13, 36)	0.8007

NIV = noninvasive ventilation.
Data are expressed as number (percentage) or median (interquartile range). Comparisons between groups are made using Fisher exact test.

score and each baseline covariate included in the matching and iteratively directs the search toward the matches that maximizes the balance of the covariates included in the analysis (i.e., makes the multivariate distribution of covariates in the matched "control" and "intervention" groups as similar as possible) (29–31). GenMatch does not drop observations that cannot be exactly matched but seeks to make the multivariate distribution of covariates in the matched groups as similar as possible and thus avoids the manual process of checking covariate balance in the matched samples and then respecifying the propensity score accordingly (29–31). In comparison to propensity score matching, GenMatch achieves the best covariate balance (32) and minimizes bias related to data replacement or arbitrary caliper matching (33).

Caution must be exercised in generalizing results of the present study. First, institutional review boards refused to authorize a randomized clinical trial due to the limited amount of information regarding the use of $ECCO_2R$ in patients with COPD. The high number of patients who refused consent to "NIV-plus-$ECCO_2R$" confirms the lack of equipoise existing at the moment the study was performed (34). Although appropriate design of matched cohort study may minimize the risk of systematic overestimation of the magnitude of the treatment, the nonrandomized design remains the major limitation of the present study (35). To minimize overestimation of the treatment effect, decision to intubate was taken by clinicians not involved in the study using predefined criteria that were 1) objective; 2) coherent with those implemented in the previous studies used to create the dataset for matched cohort analysis (23, 24); and 3) consistent with the current literature (6, 25, 26). However, since severe hypercapnia and respiratory acidosis were the most common indications for intubation (see Online data supplement, Supplemental Digital Content 1, http://links.lww.com/CCM/B63), the use of a surrogate marker of outcome that is directly influenced by the intervention (i.e., Co_2 removal) may confound interpretation of our results. Furthermore, the decisions for intubation may be biased since application of $ECCO_2R$ was unblinded. The observation of a survival benefit following use of $ECCO_2R$ suggests that mortality should be the outcome variable of future randomized clinical trials. Second, 13 patients (52%) experienced adverse events associated to the use of $ECCO_2R$. Major bleeding episodes were observed in three patients, and one patient experienced vein perforation at cannula insertion. Malfunctioning of the system caused all other adverse events. These side effects of $ECCO_2R$ should not have impact on clinical outcomes, since hospital mortality was lower in "NIV-plus-$ECCO_2R$" than in the "NIV-only." Third, we could have included patients with COPD who are not representative of those commonly admitted to the ICU for treatment with NIV as the rate of intubation and in-hospital mortality in our dataset were significantly higher than those normally observed (1). Fourth, this study is lacking long-term outcome of patients treated with "NIV-plus-$ECCO_2R$."

This study first provides a systematic evaluation of the risk-benefit profile of $ECCO_2R$ in comparison with a control group of patients with COPD at high risk of NIV failure. Results of the present investigation provide the rationale for the future randomized clinical trials that are required to validate the use of $ECCO_2R$ in patients with hypercapnic respiratory failure and respiratory acidosis nonresponsive to NIV. The observation that the reduction in intubation rate was concomitant to an almost 50% prevalence of $ECCO_2R$-related side effects may suggest that

TABLE 4. Complications Observed in the 25 Patients Treated With "Noninvasive Ventilation-Plus-Extracorporeal Co_2 Removal"

Mechanical events
Patient 2 clots in the circuit
Patient 6 clots in the circuit
Patient 9 clots in the circuit
Patient 14 clots in the circuit
Patient 16 membrane lung failure
Patient 18 pump malfunction
Patient 19 clots in the circuit
Patient 22 clots in the circuit
Patient 25 pump malfunction
Patient-related events
Patient 1 significant bleeding (hematuria)
Patient 4 significant bleeding (retroperitoneal hematoma)
Patient 13 vein perforation at cannula insertion
Patient 23 significant bleeding (groin)

TABLE 5. Operational Characteristics of Extracorporeal Co_2 Removal

Blood flow (mL/min)	255 (78)
Time of utilization (hr)	29 (5)
Heparin (IU/kg)	13.8 (3.5)
Activated partial thromboplastin time ratio	1.88 (0.66)

Data are expressed as mean (SD).

primary endpoint of future randomized clinical trials should be long-term mortality rather than intubation rate.

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