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SYSTEMATIC REVIEW

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Extracorporeal carbon dioxide removal in patients with chronic obstructive pulmonary disease: a systematic review

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Abstract *Introduction:* Extracorporeal carbon dioxide removal ($ECCO_2R$) has been proposed for hypercapnic respiratory failure in chronic obstructive pulmonary disease (COPD) exacerbations, to avoid intubation or reduce length of invasive ventilation. Balance of risks, efficacy, and benefits of $ECCO_2R$ in patients with COPD is unclear. *Methods:* We systematically searched MEDLINE and EMBASE to identify all publications reporting use of $ECCO_2R$ in COPD. We looked at physiological and clinical efficacy. A favorable outcome was defined as prevention of intubation or successful extubation. Major and minor complications were compiled. *Results:* We identified 3123 citations. Ten studies (87 patients), primarily case series, met inclusion criteria. $ECCO_2R$ prevented intubation in 65/70 (93 %) patients and assisted in the successful extubation of 9/17 (53 %) mechanically ventilated subjects. One case–control study matching to noninvasively ventilated controls reported lower intubation rates and hospital mortality with $ECCO_2R$ that trended toward significance. Physiological data comparing pre- to post-$ECCO_2R$ changes suggest improvements for pH (0.07–0.15 higher), $PaCO_2$ (25 mmHg lower), and respiratory rate (7 breaths/min lower), but not PaO_2/FiO_2. Studies reported 11 major (eight bleeds requiring blood transfusion of 2 units, and three line-related complications, including one death related to retroperitoneal bleeding) and 30 minor complications (13 bleeds, five related to anticoagulation, and nine clotting-related device malfunctions resulting in two emergent intubations). *Conclusion:* The technique is still experimental and no randomized trial is available. Recognizing selection bias associated with case series, there still appears to be potential for benefit of $ECCO_2R$ in patients with COPD exacerbations. However, it is associated with frequent and potentially severe complications. Higher-quality studies are required to better elucidate this risk–benefit balance.

Keywords Hypercapnia · Acute respiratory failure · Noninvasive ventilation

Introduction

Chronic obstructive pulmonary disease (COPD) is a major, worldwide health burden. It is currently the fourth leading cause of death and will likely become the third leading cause of death worldwide by 2030 [1]. The chronic and progressive nature of COPD is commonly aggravated by exacerbations. Each exacerbation reflects

disease progression, decreased quality of life, and an increased risk of death [2–4]. Classically, respiratory failure in COPD has been managed with noninvasive ventilation (NIV) [5], and NIV compared to invasive mechanical ventilation has been demonstrated to reduce mortality by almost half [6]. However, approximately one-quarter to one-half of these patients will fail NIV and require invasive mechanical ventilation (IMV) [7, 8]. The need for IMV heralds a poor prognosis for COPD exacerbations with in-hospital survival rates that range from 30 to 75 % [9, 10]. The subset of patients who require IMV are also at increased risk of failed weaning and prolonged ventilation [10, 11].

Extracorporeal carbon dioxide removal ($ECCO_2R$) devices have been proposed as an adjunct in patients with both hypoxic and hypercapnic respiratory failure. $ECCO_2R$, as an experimental adjunct to mechanical ventilation in patients with hypercapnic acute respiratory failure secondary to COPD exacerbations, has been utilized to avoid intubation or reduce the length of invasive ventilation. The technology is not new; it was first used in patients by Gattinoni in the 1980s [12, 13], but has not achieved wide clinical use in part because of a high rate of complications. The general principle consists of an extracorporeal circuit similar to a continuous veno-venous hemofiltration circuit but with a membrane allowing the elimination of carbon dioxide (CO_2) from the blood. In comparison with veno-venous extracorporeal membrane oxygenation (ECMO) (allowing blood oxygenation in addition to CO_2 removal), much lower blood flows are required with $ECCO_2R$ (300–1500 mL/min vs 3–5 L/min for ECMO), which allow the use of smaller vascular cannulas (ca. 14–18 Fr). However, as a result of the high risk of clotting, anticoagulation is needed. The risks and benefits of $ECCO_2R$ in patients with COPD exacerbations are yet to be fully elucidated.

The majority of $ECCO_2R$ literature describes its use in acute respiratory distress syndrome (ARDS) to allow very small tidal volume ("ultra-protective ventilation") [14–18]. In this situation, $ECCO_2R$ counteracts hypercapnia induced by very low minute ventilation. Limited studies have examined its efficacy and safety in hypercapnic respiratory failure secondary to COPD exacerbations. Therefore, we undertook a systematic review to identify all the publications reporting the use of $ECCO_2R$ devices in patients with exacerbations of COPD to determine the efficacy and safety of these devices in this disease.

Methods

Design

We conducted a systematic review with prespecified selection and outcome criteria. No review protocol was separately published. We systematically searched multiple sources to identify all the publications reporting the use of $ECCO_2R$ devices in patients with exacerbations of COPD. We searched the electronic databases Medline and Embase for articles and abstracts published before August 2014 using the following keywords: ECCOR, $ECCO_2R$, CO_2 removal, and extracorporeal. We also searched the bibliographies of included studies and review articles. We included articles published online at that time or published later in print. We searched the Clinical Trials Registry Database (http://clinicaltrials.gov) for registered unpublished and ongoing studies related to $ECCO_2R$ and COPD. No language restrictions were applied. We included a study or a case report if at least 1 adult (over 18 years) patient with COPD was treated using $ECCO_2R$. Our primary outcomes of interest were the occurrence of a favorable outcome defined as the prevention of intubation in patients receiving NIV, or successful extubation when the device was implemented after intubation. Secondary clinical outcomes included ICU and hospital mortality and length of stay. Complications were classified as follows: major (death or life-threatening conditions in the absence of treatment, directly related to a device complication; transfusion of at least 2 units of packed red cells; or the need for open surgery) or minor (bleeding requiring less than 2 units of packed red cells; transient thrombocytopenia (at most 90×10^9/L) without clinical consequence; or non-life-threatening event related to catheter insertion). Physiological outcomes included changes in the respiratory parameters, including pH, arterial partial pressure of carbon dioxide ($PaCO_2$) in mmHg, respiratory rate (RR) in breaths per minute; and changes in PaO_2/FiO_2 (the fraction of inspired oxygen) in mmHg as a measure of oxygenation.

Study selection

Two authors (MS and FB) independently reviewed the retrieved abstracts and assessed eligibility. Full-text review was conducted when either of the reviewers of the abstracts felt that the citations might meet inclusion criteria. Disagreement was resolved by consensus with a third author (LB).

Data extraction

Data from included studies were independently extracted by MS, FB, CK, and JF. We extracted the following data: study design, study and participant characteristics, study device, mode of extracorporeal access, device type, mode of ventilator support, study intervention, relevant outcome data, duration of $ECCO_2R$ use, and complications. All included studies were assessed for bias using the Cochrane Collaboration risk of bias tool [19].

Data analysis

Because most of the retrieved studies were case reports and case series without control patients, the proportion of $ECCO_2R$ patients with favorable clinical outcomes (prevention of intubation or successful extubation) and with complications were described but not pooled. Similarly the secondary clinical outcomes, ICU and hospital mortalities and lengths of stay, were also not pooled. Changes in physiological outcomes (pH, $PaCO_2$, RR, PaO_2/FiO_2) comparing pre-initiation values separately to values at 1, 6, and 24 h after initiation of $ECCO_2R$ were pooled by calculating the differences in values for each physiological outcome for individual patients before and after $ECCO_2R$, when available, and then calculating the means and standard deviations of these differences. When only group means and standard deviations were available for pre- and post-$ECCO_2R$ values, the difference was calculated and the standard deviation of the difference in means was calculated assuming a correlation (ρ) of 0.6. This was based on calculated ρ values ranging between 0.5 and 0.7 in the studies that provided individual patient pre- and post-$ECCO_2R$ values. Sensitivity analyses using both a high degree of correlation ($\rho = 0.9$) and no correlation ($\rho = 0$) resulted in no significant changes for any of the analyses. Medians and interquartile ranges [20] or ranges [21] were converted to means and standard deviations using previously published methods, where necessary [20]. Trial results were pooled using the generic inverse variance weighting method in Review Manager (RevMan version 5.2; Cochrane Collaboration, Oxford, UK) with a two-sided significance level of 5 %. Individual trial and summary results are reported with 95 % confidence intervals (CIs). Random effects models which incorporate between-trial heterogeneity and give wider and more conservative CIs when heterogeneity is present were used for all analyses [22]. Statistical heterogeneity among trials was assessed using the I^2 statistic, defined as the percentage of total variability across studies attributable to heterogeneity rather than chance, and using published guidelines for low ($I^2 = 25$–49 %), moderate ($I^2 = 50$–74 %), and high ($I^2 \geq 75$ %) heterogeneity [23]. Z tests of interaction were used to calculate interaction p values comparing pooled changes from pre-$ECCO_2R$ between later and earlier times after $ECCO_2R$ initiation (i.e., comparing the changes from pre-$ECCO_2R$ at 6 vs 1 h, and 24 vs 6 h).

Results

Search results

Our search strategy identified 3123 citations. Of these, 2085 were removed from the analysis for not meeting screening eligibility. Thirty-eight studies were extracted for full-text analysis, of which ten studies met inclusion criteria and were subsequently analyzed in detail (Supplementary Fig. 1).

Pending and/or ongoing clinical studies

We identified five ongoing studies related to $ECCO_2R$ and COPD [24–28] on clinicaltrials.gov. A planned randomized controlled trial by Barrett [24] (target $N = 24$) will assess the time to cessation of NIV with the use of $ECCO_2R$ as an adjunct to NIV in acute exacerbations of COPD. Nava has two ongoing prospective cohort studies, one of which will attempt to facilitate weaning in mechanically ventilated hypercapnic respiratory failure patients with the use of carbon dioxide removal [25] (target $N = 15$), while the other will facilitate reduction in $PaCO_2$ in stable COPD patients with chronic hypercapnic respiratory failure not responding to chronic NIV [26] (target $N = 15$). The ongoing prospective cohort ECLAIR study will use $ECCO_2R$ to prevent intubation in patients with acute hypercapnic respiratory failure failing NIV [27] (target $N = 30$). Finally, the PALP-COPD randomized controlled trial (target $N = 120$) aims to facilitate extubation of patients with COPD exacerbations with the aid of $ECCO_2R$ [28].

Characteristics of included studies

In total, ten studies reporting on 87 patients were included in this systematic review (Table 1). This included three single-patient case reports, two of which used $ECCO_2R$ in patients on NIV to avoid intubation [29, 30] and one in a mechanically ventilated patient to facilitate extubation [31]; four case series reporting on five invasively ventilated patients [32] and five [33], two [34], and six [35] patients receiving NIV, respectively. It also included three larger studies. One was a 20-patient case series that included seven patients on NIV at high likelihood of requiring mechanical ventilation, and two patients on NIV and 11 patients already on IMV who failed previous weaning attempts [36]. The other two were case control studies that compared 25 prospective $ECCO_2R$-treated NIV patients with 21 matched NIV historical control patients [37]; and 21 retrospective $ECCO_2R$-treated NIV patients from four centers with 21 matched control patients treated in one of the four centers over the same time period who had failed NIV and required mechanical ventilation [38].

Table 2 describes the device characteristics and the anticoagulation targets, when described. All studies implemented a pump-driven veno-venous $ECCO_2R$ device except the study by Kluge [38] that used the pumpless arteriovenous Novalung iLA device. Blood flow

Table 1 Studies included in systematic review with design, outcome, and complication data

References	Design	Patients	Clinical outcomes			Adverse events
			Intubation/extubation	Mortality	Length of stay (days)	
Case control studies						
Del Sorbo [37]	Prospective cases matched with historical controls using multivariate matching software (GenMatch)	$n = 25$ NIV + $ECCO_2R$ vs $n = 21$ NIV	22/25 (88 %) vs 14/21 (67 %) Avoided intubation (HR for requiring intubation 0.27, 95 % CI 0.07–0.98, $p = 0.047$)	Hospital: 2/25 (8 %) vs 8/21 (35 %) ($p = 0.035$)	ICU: 8 (IQR 7–10) vs 12 (IQR 6–15) ($p = 0.19$) Hospital: 24 (IQR 21–28) vs 22 (IQR 13–36) ($p = 0.80$)	Major complications: 4 3 major bleeds (requiring ≥2 units pRBC transfusion; 1 resulted in endotracheal intubation due to hemodynamic instability from retroperitoneal bleeding) 1 venous perforation at insertion site Minor complications: 9 6 clots in circuit (leading to immediate endotracheal intubation in 2 patients) 2 pump malfunction 1 membrane lung failure
Kluge [38]	Retrospective, cases (4 sites) matched with contemporaneous controls (from only 1 of the sites) based on diagnosis, age ± 10 years, SAPS II ± 6 at ICU admission, and pH ± 0.05[a] before $ECCO_2R$ or intubation	$n = 21$ NIV + $ECCO_2R$ vs n = 21 failed NIV requiring invasive ventilation	NIV + $ECCO_2R$ 19/21 avoided intubation	28 day: 5/21 (24 %) vs 4/21 (19 %) (*adj* $p = 0.85$) 6 month: 7/21 (33 %) vs 7/21 (33 %) (*adj* $p = 0.90$)	ICU: 15 (r. 4–137) vs 30 (r. 4–66) (*adj* $p = 0.26$) Hospital: 23 (r. 4–137) vs 42 (r. 4–248) (*adj* $p = 0.06$)	Major complications: 2 2 major bleeds (requiring ≥2 units pRBC transfusion) Minor complications: 9 7 minor bleeds 1 femoral artery pseudoaneurysm 1 HIT
Case series: both avoidance of intubation and successful extubation						
Burki [36]	Case series	$n = 9$ NIV +ECCOR plus $n = 11$ invasive ventilation + $ECCO_2R$ (no control)	Group 1: 7/7 acute NIV + $ECCO_2R$ avoided intubation Group 2: 2/2 difficult-to-wean NIV + $ECCO_2R$ avoided intubation Group 3: 3/11 invasive ventilation + $ECCO_2R$ successfully extubated			Major complications: 5 1 death related to retroperitoneal bleeding 1 pneumothorax 3 major bleed (requiring ≥2 units pRBC transfusion) Minor complications: 3 2 thrombocytopenia 1 DVT
Case series and case reports: avoidance of intubation						
Bonin [29]	Case report	$n = 1$ NIV + $ECCO_2R$ No control	1/1 avoided intubation			1 minor complication 1 minor bleed
Burki [33]	Case series	$n = 5$ NIV + $ECCO_2R$ No control	5/5 avoided intubation			3 minor complications 1 minor bleed 1 thrombocytopenia 1 transient hypotension

Table 1 continued

References	Design	Patients	Clinical outcomes			Adverse events
			Intubation/extubation	Mortality	Length of stay (days)	
Crotti [30]	Case report	$n = 1$ NIV	1/1 avoided intubation			Not evaluated
Mani [34]	Case series	$n = 2$ NIV + $ECCO_2R$	2/2 avoided intubation			Minor complications: 1 1 thrombocytopenia
Spinelli [35]	Case series	$n = 6$ NIV + $ECCO_2R$	6/6 avoided intubation			Not evaluated
Case series and case reports: successful extubation						
Abrams [32]	Case series	$n = 5$ invasive ventilation + $ECCO_2R$	5/5 successfully extubated	ICU: 0/5 (0 %)	ICU: 10.2 ± 2.5	4 minor complications: 2 minor bleeds
		No control	Before initiation of $ECCO_2R$, all five subjects failed NIV	Hospital: 0/5 (0 %)	Hospital: 15.6 ± 8.6	2 related to anticoagulation
Cardenas [31]	Case report	$n = 1$ invasive ventilation + $ECCO_2R$ (no control)	1/1 successfully extubated			None reported

Mean ± SD

adj adjusted, *DVT* deep vein thrombosis, *$ECCO_2R$* extracorporeal removal of carbon dioxide, *HIT* heparin-induced thrombocytopenia, *ICU* intensive care unit, *IQR* interquartile range, *NIV* noninvasive ventilation, *$PaCO_2$* partial arterial pressure of carbon dioxide, *pRBC* packed red blood cell, *r.* range, *SAPS II* Simplified Acute Physiology Score II

[a] Despite close match in pH (within 0.01), $PaCO_2$ before intubation or $ECCO_2R$ initiation was higher in the $ECCO_2R$-treated group (84 vs 65 mmHg, $p = 0.001$). Also a higher percentage of patients were awaiting lung transplant in the $ECCO_2R$-treated group (43 vs 0 %)

parameters varied significantly among the studies, ranging from several hundred milliliters per minute to several liters per minute. Vascular cannulas ranged from 13 to 23 Fr, though many used a 15.5-Fr catheter with the Hemolung device. Anticoagulation targets were measured either by the activated partial thromboplastin time test (aPTT) or the activated clotting time test (ACT). Intravenous unfractionated heparin was used for anticoagulation.

Inclusion and exclusion criteria for $ECCO_2R$

Inclusion and exclusion criteria for $ECCO_2R$ were documented in four studies: Del Sorbo [37], Kluge [38], Burki [36], and Abrams [32] (Table 3). In general, the indications for $ECCO_2R$ included hypercapnic respiratory failure with clinical and laboratory evidence of worsening acid–base and respiratory parameters. Contraindications were more heterogeneous but included bleeding diathesis, thrombocytopenia, and inability to cannulate a central vein or central nervous system pathology.

Risk of bias

Since none of the studies meeting inclusion criteria were randomized controlled trials, the risk of bias of all studies was high with the exception of the Del Sorbo [37] trial which we graded as moderate (Supplemental Table 1).

Effect of interventions

Primary outcome

Eight studies presented data on intubation prevention [29, 30, 33–38] (Table 1). Seventy patients were included in the analysis on intubation prevention with an overall success rate of 65/70 (92.8 %) (Supplemental Fig. 3). The two case reports [29, 30] and three small case series [33–35] all reported a perfect success rate of preventing intubation when patients were placed on $ECCO_2R$, as did the larger case series of Burki et al. [36]. In the study by Kluge et al. [38], 2/21 (10 %) $ECCO_2R$-treated NIV patients required IMV, compared to 21/21 (100 %) of the control patients. Finally, in the case–control study by Del Sorbo et al. [37], only 3/25 patients (12 %, 95 % CI 3–31 %) in the NIV + $ECCO_2R$ group required intubation [due to device clotting ($n = 2$) or hemodynamic instability from retroperitoneal bleeding ($n = 1$)] vs 7/21 (33 %, 95 % CI 15–57 %) in the matched NIV-only group (HR 0.27, 95 % CI 0.07–0.98, $p = 0.047$).

$ECCO_2R$ was utilized in 17 patients receiving IMV across one case report [31], one case series ($n = 5$) [32], and 11 patients from the Burki study [36]. The rate of successful extubation in this cohort was 9/17 (52.9 %)

Table 2 Device characteristics and anticoagulation strategies

References	Device	Cannula size (Fr)	Blood flow (mL/min)	Anticoagulation target	Duration of support (days)
Del Sorbo [37] ($n = 21$)	Hemodec V–V	14	255 ± 78	aPTT (1.88 ± 0.66) × normal	1.21 ± 0.20
Kluge [38] ($n = 21$)	Novalung A–V	13–17	1100 (range 600–1800)	aPTT range 1.5–1.8 × normal	Median 9 (range 1–116)
Burki [36] ($n = 20$)	Hemolung (ALung) V–V	15.5	431 ± 74 (range 117–587)	aPTT 1.5–2.3 × normal	4.3 ± 2.5 (range 0.01–8)
Bonin [29] ($n = 1$)	Hemolung (ALung) V–V	15.5	Range 422–520	aPTT 1.5–2.3 × normal	6
Burki [33] ($n = 5$)	Hemolung (ALung) V–V	15.5	467 ± 130	Not reported	Not reported
Crotti [30] ($n = 1$)	Maquet V–V	Not reported	2000	Not reported	6
Mani [34] ($n = 2$)	Hemolung (ALung) V–V	15.5	Range 350–550	ACT1.2–1.6 × normal	Mean 3
Spinelli [35] ($n = 6$)	Device not reported V–V	Not reported	2900 ± 500	Not reported	Not reported
Abrams [32] ($n = 5$)	Maquet V–V	20–23	Range 1000–1700	aPTT 1.3–2 × normal	8 ± 3.2
Cardenas [31] ($n = 1$)	Maquet V–V	18	800	ACT 1.5–1.7 × normal	4

All studies used unfractionated intravenous heparin for anticoagulation. Normal aPTT taken as 30 s and normal ACT as 120 s. Data are presented as mean ± SD except where noted otherwise

(Supplemental Fig. 2). The single patient in the case report and all five patients in the small case series were successfully extubated following the implementation of $ECCO_2R$, but Burki's study successfully extubated only 3/11 (27 %).

Secondary clinical outcomes

Secondary clinical outcomes include ICU and hospital mortality and length of stay. Three studies presented data on mortality. Del Sorbo et al. [37]. found significantly reduced hospital mortality in patients receiving $ECCO_2R$ compared to controls (8 % in the $ECCO_2R$ group vs 35 % in the NIV alone group, $p = 0.035$). The case series by Abrams et al. [32] demonstrated a 100 % survival rate both to ICU discharge and hospital discharge in their uncontrolled series of five patients. Finally, Kluge et al. [38], in their two retrospectively compared groups, showed no significant difference in mortality at 28 days (19 % with $ECCO_2R$ vs 24 % without $ECCO_2R$) or 6 months (both groups 33 %).

These same three studies presented length of stay data. Del Sorbo et al. [37] found nonsignificant differences in either ICU [8 (7, 10) vs 12 (6, 15); $p = 0.19$] or hospital length of stay [24 (21, 28) vs 22 (13, 36); $p = 0.80$] in their study groups (data presented as median (interquartile range), $ECCO_2R$ vs no $ECCO_2R$). Similarly, Kluge et al. [38] found no differences in either median ICU or hospital length of stay in their $ECCO_2R$ vs invasive ventilation groups (15 vs 30 days and 23 vs 42 days, respectively). Abrams et al.'s [32] case series reported an average ± standard deviation ICU length of stay of 10.2 ± 2.5 days and a hospital length of stay of 15.6 ± 8.6 days.

Respiratory parameters

Compared to baseline, initiation of $ECCO_2R$ very quickly and significantly improved pH (Fig. 1a and Supplemental Fig. 4a), $PaCO_2$ (Fig. 1b, Supplemental Fig. 4b), and RR (Fig. 1c, Supplemental Fig. 4c), even after the first hour; pH increased by 0.07 (95 % CI 0.06–0.09, $p < 0.001$; three studies [34, 37, 38], 48 patients) after 1 h, 0.11 (95 % CI 0.10–0.11, $p < 0.001$; three studies [34, 36, 38], 29 patients) after 6 h, and 0.15 (95 % CI 0.10–0.20, $p < 0.001$; four studies [32, 34, 36, 38], 33 patients) after 24 h. There was no between-study heterogeneity in the 1-h and 6-h comparisons ($I^2 = 0$ %), but a high degree of heterogeneity in the 24-h comparison ($I^2 = 93$ %). The greater increase between 1 and 6 h was statistically significant (interaction $p = 0.0005$) but the increase between 6 and 24 h did not achieve statistical significance (interaction $p = 0.06$). $PaCO_2$ decreased around 25 mmHg similarly between 1 and 6 h, and between 6 and 24 h

Table 3 Inclusion and exclusion criteria for $ECCO_2R$

References	Inclusion	Exclusion
Del Sorbo [37]	≥2 h of NIV with pH < 7.30 and $PaCO_2$ > 20 % above baseline and RR > 30 with accessory muscle use or paradoxical breathing	MAP < 60 mmHg Platelets <30 × 10^9/L INR > 1.5 Bleeding diathesis, central nervous system pathology within previous 3 months, epidural catheter, gastrointestinal bleeding within the previous 6 weeks, varices, chronic jaundice/cirrhosis/ascites, trauma Body weight >120 kg
Kluge [38]	Worsening respiratory acidosis and oxygenation, increasing RR, and clinical signs suggestive of respiratory muscle fatigue and/or increased work of breathing despite NIV	None provided, but unable to cannulate 3 patients due to too severe peripheral vascular disease
Burki [36]	≥1 h of NIV with $PaCO_2$ > 55 and pH < 7.25, or pH < 7.30 and $PaCO_2$ > 55 with <5 mmHg $PaCO_2$ decrease from baseline following NIV application	Hemodynamic instability, sensitivity to heparin, recent major surgery, uncontrolled arrhythmia, thrombocytopenia (platelets <100 × 10^9/L), bleeding diathesis, coma
Abrams [32]	Exacerbation of COPD, respiratory failure with an ongoing requirement for NIV, and a preintubation arterial blood gas (ABG) with pH < 7.35 and PaCO2 > 55 mm Hg	NYHA class IV functional status or evidence of decompensated congestive heart failure, advanced malignancy, body mass index greater than 31.1 kg/m^2 for men or greater than 32.2 kg/m^2 for women, acquired immunodeficiency syndrome or other severely immunocompromised condition, PaO_2 to FiO_2 ratio consistently less than 250 mmHg, history of intracranial bleeding, known or suspected pregnancy, history of complications from extracorporeal support, inability to receive blood products, known hypersensitivity to heparin or history of heparin-induced thrombotic thrombocytopenia, inability to ambulate within 7 days before hospital admission anatomic abnormalities that would preclude catheter placement in the neck, severe bleeding diathesis, severe malnutrition or cachexia, and severely debilitated state

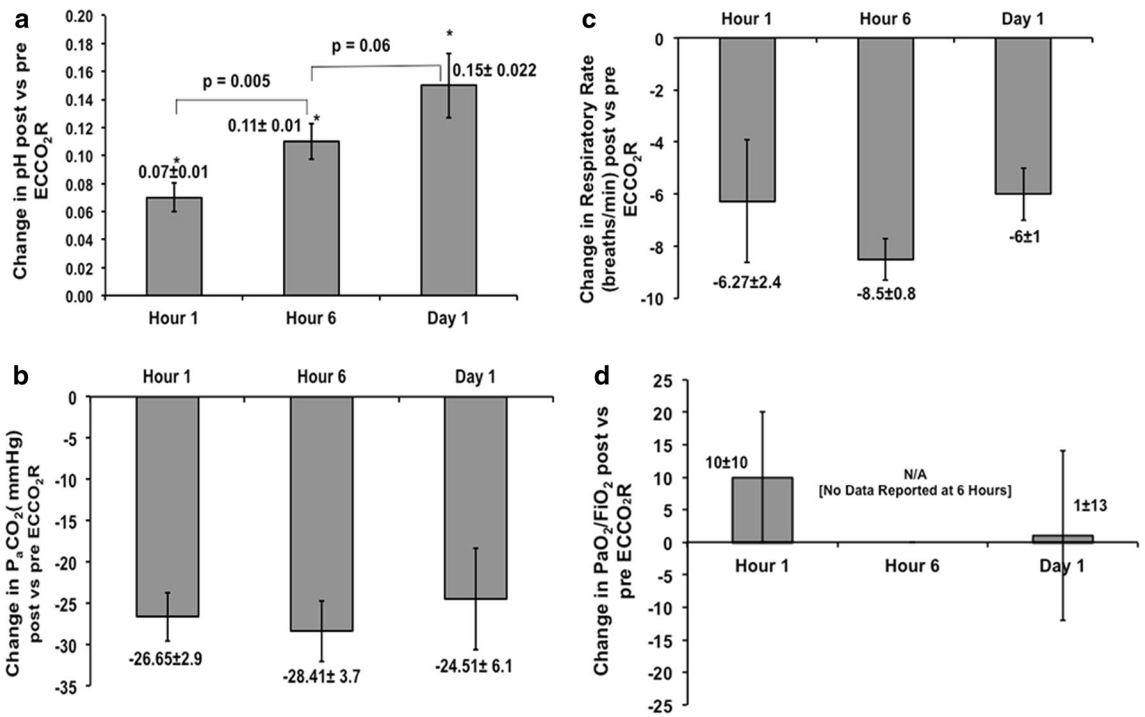

Fig. 1 Physiological parameters, data expressed as mean ± SD. **a** pH Overall change in pH was 0.07–0.15 increase; $p < 0.00001$, $^*p < 0.001$ at each time measurement vs pre-$ECCO_2R$; $p = 0.005$ for interaction 1 vs 6 h, $p = 0.06$ for interaction 6 h vs 1 day. **b** Overall decrease in $PaCO_2$ was 24–26 mmHg vs pre-$ECCO_2R$, $p \leq 0.0009$. **c** Overall change in respiratory rate was 6–8 breaths/min lower vs pre-$ECCO_2R$, $p \leq 0.008$. **d** No significant change in PaO_2/FiO_2 1 h or 1 day vs pre-$ECCO_2R$

(interaction $p > 0.05$) with moderate to high heterogeneity in the 1-h and 24-h comparisons ($I^2 = 55$ and 77 %, respectively) (Fig. 1b). Few studies reported RR (only one study reported 6-h and 24-h data). Decreases of around 6–8 breaths per min were similar at all time points (interaction $p \geq 0.05$) with high between study heterogeneity at 1 h ($I^2 = 93$ %), the only comparison with data from more than one study. PaO_2/FiO_2 was reported only in single studies at 1 h [37] and 24 h [38], thereby precluding pooling, and was not significantly changed by $ECCO_2R$ (Fig. 1d; Supplemental Fig. 4d).

Only one study compared physiological values in patients treated with $ECCO_2R$ to matched controls. This matched case–control study reported statistically significant improvements at 1 h in pH by 0.06 ($p = 0.0003$), $PaCO_2$ by 17 mmHg ($p = 0.01$), and RR by 5 breaths/min ($p = 0.0002$), and a worsening in PaO_2/FiO_2 by 57 mmHg ($p = 0.0006$) [37].

Complications

All but two studies [30, 35] reported on $ECCO_2R$-related complications (these two case reports did not report any information on complications). We found a total of 11 major and 30 minor complications in the included studies (Table 1; Fig. 2). Of the major complications, 8/11 (72.7 %) (Table 1) were clinically significant bleeding episodes requiring at least 2 units of packed red cells (with one patient requiring endotracheal intubation due to hemodynamic instability from retroperitoneal bleeding). The three remaining major complications consisted of one venous perforation at the catheter insertion site, one pneumothorax, and one death related to a retroperitoneal bleed secondary to perforation of an iliac vein.

Of the 30 minor complications (Table 1) we found 13 minor bleeding episodes related either to device insertion or due to systemic anticoagulation. There were four episodes of transient thrombocytopenia and one occurrence of heparin-induced thrombocytopenia. There was one reported deep venous thrombosis, one femoral artery pseudoaneurysm, and one episode of transient systemic hypotension. Nine complications were related to device malfunction in the form of circuit clotting ($n = 6$), pump malfunction ($n = 2$), and membrane failure ($n = 1$), two of which resulted in emergent intubations.

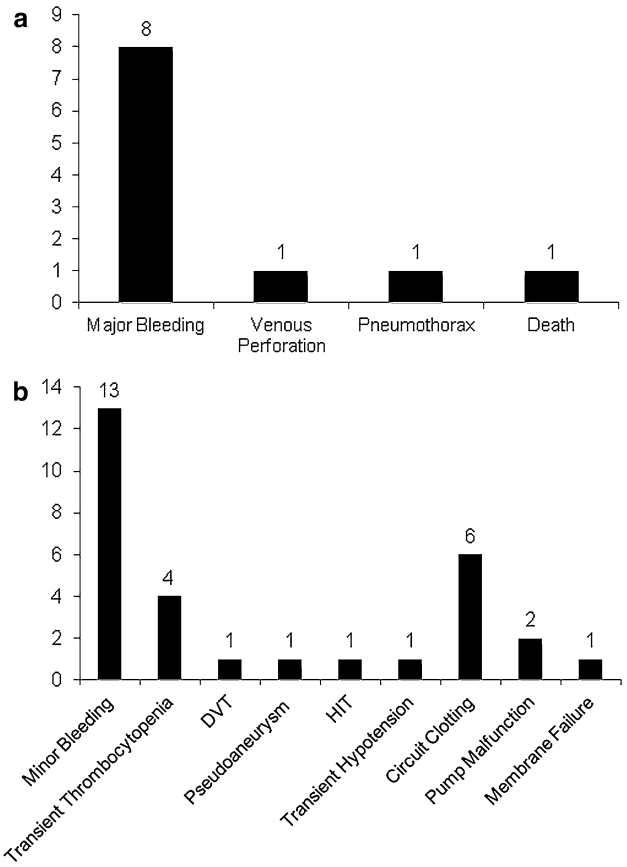

Fig. 2 Distribution of complications: **a** Major and **b** minor complications. *DVT* deep venous thrombosis

Discussion

This exhaustive systematic review evaluated the efficacy and safety of the experimental use of $ECCO_2R$ in 87 patients with hypercapnic respiratory failure across ten studies, primarily from cases series and case reports [29–36], and two studies which matched patients treated with $ECCO_2R$ to historical controls [37, 38]. The overall level of evidence of the studies included is of relatively low quality, but this review still provides an estimate of $ECCO_2R$-related physiological changes and complications. The majority of patients in this review were either successfully weaned from mechanical ventilation or sustained on NIV, avoiding intubation. These high success rates, however, must be interpreted very cautiously given the clear selection bias associated with case series data.

The data presented in the included studies were quite heterogeneous. Outside our primary outcome, only three studies presented data on ICU and hospital length of stay and mortality. The available physiological data, comparing primarily pre- to post-$ECCO_2R$ changes in the same patients, suggest rapid and sustained improvements in ventilatory parameters including pH, $PaCO_2$, and respiratory rate, but not in oxygenation as measured using PaO_2/FiO_2. On the basis of limited data, pH continued to improve between 1 and 24 h post initiation, whereas $PaCO_2$ and respiratory rate did not show significant further improvements after 1 h. If this finding based on

limited data is accurate, this suggests that the improvement in pH between 1 and 24 h may be attributable to improvements in metabolic rather than respiratory acidosis which could be due to factors such as improved circulation (reducing possible elevated lactate) or administration of diuretics or buffers (e.g., citrate loading from massive blood transfusions). Unfortunately, the included studies did not provide enough additional data to test these hypotheses. It should be noted that these changes in physiological outcomes over time did not account for other ventilatory changes made by clinicians in response to the early improvements observed with $ECCO_2R$ initiation, as these were generally not provided in the study reports.

The technical characteristics of $ECCO_2R$ have potential advantages over ECMO, but these foreseeable gains may give rise to significant harm. A recent editorial by Brochard [39] highlights this controversy. The major advantage of $ECCO_2R$ compared to ECMO is the considerably lower blood flow required: several hundred milliliters per minute vs several liters per minute for ECMO. The lower flow allows for the use of vascular cannulas similar in size to those used in continuous veno-venous hemofiltration (approximately 14–18 Fr, depending on device, in $ECCO_2R$ vs upwards of 20 Fr in ECMO). However one risk of the low flow $ECCO_2R$ system is the risk of membrane and circuit clotting related to low flow and thus the need for therapeutic anticoagulation.

Eight of the ten included studies reported on complications. The types and rates of complications again varied across the studies and there were substantially more observed complications in the larger clinical trials (32 out of 41 total recorded complications), with only nine recorded in the case report and smaller case series. Almost half of the patients in this systematic review experienced an $ECCO_2R$-related complication (41/87, 47.1 %). About half of the total complications (21/41, 51.2 %) were bleeding episodes related to anticoagulation; eight were severe hemorrhagic events while 13 were minor bleeds. Retroperitoneal bleeding following femoral cannulation led to one death [36], while another patient required intubation due to resulting hemodynamic instability [37]. Several studies in our review reported no hemorrhagic complications [30, 31, 34, 35], which highlights the small sample sizes and differing protocols in the current body of literature.

Despite full anticoagulation we found nine thrombotic complications related to device failure. As we have previously noted [39], membrane clotting or device failure during $ECCO_2R$ can be a life-threatening event, which may lead to a rapid rise in carbon dioxide and overwhelming respiratory acidosis necessitating prompt intubation of patients and/or significant changes to their respiratory support. Only in the Del Sorbo study [37] was there mention of two patients requiring intubation in the setting of decompensation secondary to membrane clotting. It is evident by the propensity for both hemorrhagic and thrombotic events that the optimal anticoagulation scheme that minimizes both of the above is yet to be fully elucidated.

The risks related specifically to central line insertion, including pneumothorax, venous perforation, accidental arterial puncture, aneurysm, hematoma formation, and infection occurred rarely in this review and this limited body of literature is insufficient to ascertain if there is an increased risk of these with $ECCO_2R$-sized cannulas. They do not seem low, however, compared to usual complication rates of central venous access or hemodialysis access [40, 41].

In several $ECCO_2R$ studies the intravascular devices and blood flow rates are comparable to those used for continuous renal replacement therapies (CRRT). One of the ongoing studies utilizes a modified continuous veno-venous hemofiltration system to provide $ECCO_2R$ [26]. This suggests that these techniques may demonstrate similar complication rates. Direct comparison of complication rates, however, is difficult because one must consider not only technical characteristics of the system but the underlying pathobiology of the patient. The types and rates of complications among CRRT studies vary but a recent review sheds some light [42]. This group's experience with 1809 patients found a total complication rate of 46 %. The authors found a bleeding rate of 2.3 %, thrombosis rate of 2.5 %, and 15 episodes (0.8 %) of pneumothorax. Accidental arterial puncture occurred 5.7 % of the time and there was an infection rate of 17.2 %. There was no mention of dialysis membrane or circuit failures. These authors do not comment on blood flows, cannula sizes, or anticoagulation doses. Although a similar overall complication rate was seen in this large review of CRRT when compared to our review of $ECCO_2R$, the distribution of complications is different and the relative contribution of circuit/system complications remains unknown.

Other sources of heterogeneity include the types of $ECCO_2R$ devices, the anticoagulation schemes, sizes of the vascular cannulas, and one study [38] that used an arterio-venous pumpless system. How these factors affect the rates of hemorrhage or thrombosis and other complication risks is not known, strengthening the need for higher-quality studies.

Limitations

Although we used rigorous systematic review and meta-analytic methods including a reproducible and comprehensive literature search strategy, clearly defined inclusion criteria, and duplicate citation review, data abstraction, and quality assessment of individual studies,

a protocol for our systematic protocol was not pre-published. In addition, we identified only low-level evidence, primarily case series data. These types of reports are at high risk of selection bias since unsuccessful case reports or series are generally not published. As a result of a lack of control groups for clinical outcomes, we were limited to pooling before–after physiological outcomes, recognizing that surrogate outcomes typically overestimate benefits in clinical outcomes [43]. In particular, the reported rates of intubation prevention and earlier extubation are likely optimistic estimates. Despite these significant limitations, this review describes and highlights the paucity of data in this field and provides practitioners with a description of how this technique has been implemented, summarizing the complications that have occurred and the changes in physiological outcomes that may be expected.

Conclusion

$ECCO_2R$ is a fascinating technology that holds theoretical promise for the treatment of hypercapnic respiratory failure in the setting of COPD exacerbations. The current body of literature demonstrates that there is a paucity of high-quality data. It suggests, however, that this experimental technology may be highly efficient from a physiological standpoint but is also not without risk; in addition to the risk associated with central line insertion, there is a delicate balance between hemorrhage and thrombosis. This analysis strongly supports the need for further research with physiological and safety studies, including randomized controlled trials to more clearly elucidate the risk–benefit balance of $ECCO_2R$ in COPD exacerbations.

Conflicts of interest No author identifies a conflict of interest.

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