

Extracorporeal CO₂ removal (ECCO₂R) in patients with stable COPD with chronic hypercapnia: a proof-of-concept study

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Abstract Domiciliary non-invasive ventilation (NIV) effectively reduces arterial carbon dioxide pressure (PaCO₂) in patients with stable hypercapnic chronic obstructive pulmonary disease, but a consistent percentage of them may remain hypercapnic. We hypothesised that extracorporeal CO₂ removal (ECCO₂R) may lower their PaCO₂. Ten patients hypercapnic despite ≥6 months of NIV underwent a 24-hour trial of ECCO₂R. Six patients completed the ECCO₂R-trial with a PaCO₂ drop ranging between 23% and 47%. Time to return to baseline after interruption ranged 48–96 hours. In four patients, mechanical events led to ECCO₂R premature interruption, despite a decreased in PaCO₂. This time window 'free' from hypercapnia might allow to propose the concept of 'CO₂ dialysis'.

INTRODUCTION

To compensate for the severe impairment of respiratory mechanics, patients with chronic obstructive pulmonary disease (COPD) decrease tidal volume and increase respiratory rate. The 'price' patients pay for this strategy is hypercapnia.¹ In stable conditions, renal and metabolic compensatory mechanisms keep pH in the physiological ranges (chronic hypercapnia).² Although, the relationship between CO₂ reduction and clinical benefit in terms of patients-related outcome measures is unclear, studies that have shown clinical benefit of non-invasive ventilation (NIV) all aimed at substantial CO₂ reduction.³ However, several patients may not tolerate chronic NIV, are not compliant with the therapy or do not respond in terms of arterial carbon dioxide pressure (PaCO₂) reduction.^{4,5}

Extracorporeal CO₂ removal (ECCO₂R) may decrease PaCO₂ and increase pH in patients with acute decompensation of COPD that do not respond to NIV thus avoiding invasive ventilation.⁶ This 'proof-of-concept' study set up to examine the hypothesis that ECCO₂R may effectively and safely lower PaCO₂ also in patients with chronic hypercapnia unresponsive to domiciliary NIV.

METHODS

Written informed consent was obtained. Patients with COPD in charge of the domiciliary NIV programme of the 'Policlinico di Sant'Orsola' (University of Bologna, Italy) and of the 'Mauro Scarlato' (Salerno Italy) hospitals were eligible for inclusion if they were older than 40 years of age, had severe COPD, were clinically stable, as assessed with monthly visit in our outpatients clinic, and had

a baseline PaCO₂ >50 mm Hg with a pH >7.35. ECCO₂R was proposed in patients enrolled in an home care NIV programme for at least 6 months, not responding in terms of PaCO₂ reduction (ie, <5% reduction relative to the daytime value observed on spontaneous ventilation before initiation of domiciliary NIV). IPAP was set at 19.3±1.7 and EPAP 4.2±0.42 cmH₂O and NIV average use was 5.8±1.1 hours/night. Patients were excluded if contraindication to ECCO₂R were present⁶ or if they had a body mass index >30 or confirmed sleep apnea syndrome.

Patients underwent a 24-hour trial of ECCO₂R during spontaneous breathing in a high intensity area of the respiratory ward using the Decap Smart (Hemodec, Salerno) and the ProLung (Estor, Pero) systems both equipped with a polypropylene membrane lung (Euroset, 1.35 m², Medolla). Heparin was administered to maintain the activated partial thromboplastin time ratio to approximately 1.5. The femoral vein was accessed via a double lumen catheter (14 F; JOLINE).⁶

Arterial blood gases and respiratory rate were recorded at baseline (time 0) and after 1, 3, 6, 12, 18 and 24 hours of ECCO₂R and every 6–8 hours after disconnection until daytime values of PaCO₂ returned at baseline level. Patients remained on spontaneous breathing until values of PaCO₂ returned to the levels at baseline. NIV was hence restored.

Potential adverse events were classified as mechanical and patient related⁶ and daily assessed for 15 days after the ECCO₂R trial. Occurrence of any adverse event during the ECCO₂R trial led to treatment interruption and catheter removal.

RESULTS

ECCO₂R was implemented in ten patients. Baseline characteristics of patients and ECCO₂R settings are shown in [table 1](#).

Twenty-four hours of ECCO₂R were completed in six patients causing a reduction in PaCO₂ ranging between 23% and 47% ([figure 1A](#)). Following interruption of ECCO₂R, the time required to return to baseline values of PaCO₂ ranged between 48 and 96 hours ([table 1](#)). In four patients, mechanical related adverse event (circuit clotting, catheter displacement and pump malfunctioning) led to ECCO₂R interruption ([figure 1B](#)) after 2–23 hours of treatment ([table 1](#)). Of note, values of PaCO₂ immediately before ECCO₂R interruption were 23%–33% lower than PaCO₂ at baseline. Values of

Table 1 Baseline values

Patients	Baseline values							ECCO ₂ R settings				
	Completed ECCO ₂ R trial	Gender	Age (years)	FEV ₁ (% of predicted)	MMRC	Charlson Index	PaCO ₂ (mm Hg)*	pH*	HCO ₃ ⁻ (mmol)*	Blood Flow (mL/min)	Heparin (IU/kg)	aPTT ratio
S.F.	M	72	26	5	4	59.2	7.47	40.0	200	16	2.20	75
P.P.	M	71	27	5	1	64.9	7.35	36.8	260	15	1.24	48
A.D.	F	68	55	3	3	89.3	7.36	40.2	250	18	2.02	96
T.M.	F	54	35	3	4	75.6	7.39	39.7	240	15	1.55	62
S.V.	M	50	48	2	2	88.5	7.43	45.2	230	16	1.39	72
C.C.	M	80	40	3	3	68.1	7.41	38.4	260	15	2.18	52
Interrupted ECCO ₂ R trial												Reasons and time of ECCO ₂ R interruption (Hours)
N.A.	F	59	40	3	2	51.7	7.41	32.8	260	16	1.52	Pump malfunction: 8 hours
A.U.	M	72	18	5	2	72.5	7.37	34.3	250	18	2.20	Clotting: 23 hours
Z.D.	F	67	23	5	3	59.3	7.42	39.5	283	18	2.15	Catheter displacement: 6 hours
B.L.	F	59	20	5	3	57.0	7.43	35.5	240	16	1.67	Pump malfunction: 2 hours

*Values obtained during non-invasive ventilation delivered in a controlled environment.

aPTT, activated partial thromboplastin time; ECCO₂R, extracorporeal CO₂ removal; FEV₁, forced expiratory volume in 1s; HCO₃⁻, bicarbonate; MMRC, modified British Medical Research Council questionnaire; PaCO₂, partial arterial pressure of carbon dioxide.

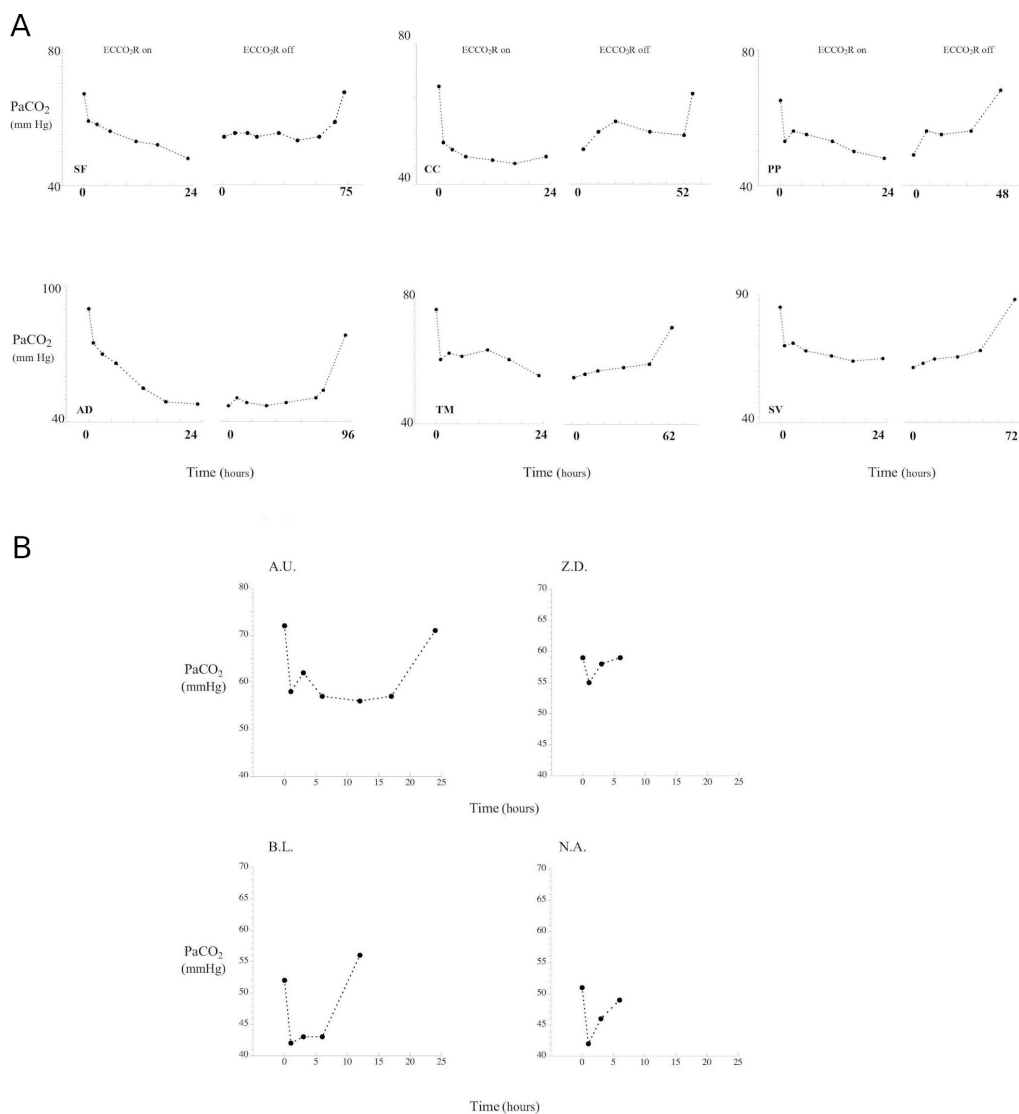


Figure 1 Individual levels of PaCO₂ during ECCO₂R in all patients completing the study (PANEL A) or interrupting the trial for a technical problem (PANEL B). ECCO₂R, extracorporeal CO₂ removal; PaCO₂, arterial carbon dioxide pressure.

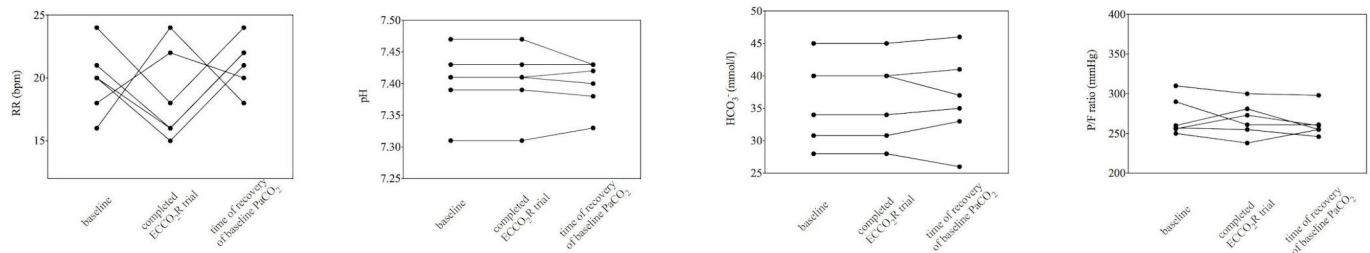
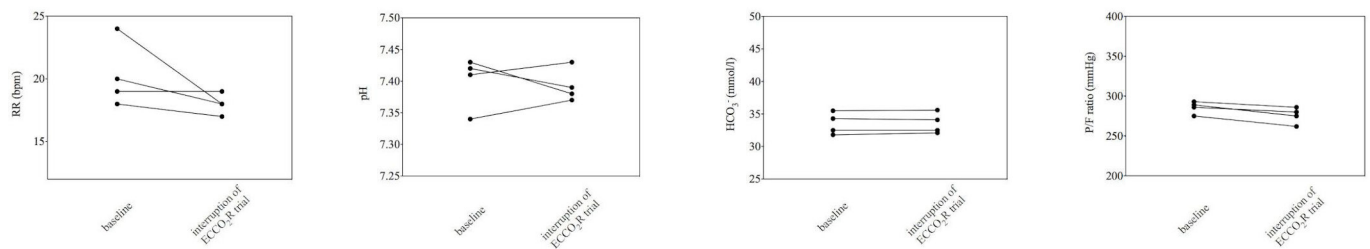
Completed ECCO₂R trialInterrupted ECCO₂R trial

Figure 2 Individual values of pH, HCO₃⁻, PaO₂/FiO₂ and respiratory rate, during ECCO₂R in representative patients completing the study (upper part) or interrupting the trial for a technical problem (lower part). ECCO₂R, extracorporeal CO₂ removal; HCO₃⁻: bicarbonate; PaO₂/FiO₂, arterial oxygen tension/fractional inspired oxygen.

pH, respiratory rate and HCO₃⁻ remained stable during the time course of the trial (figure 2).

No patient-related adverse events⁶ were observed for 15 days following ECCO₂R trial.

DISCUSSION

This study shows that it is possible to safely lower PaCO₂ with ECCO₂R in stable patients with COPD with chronic hypercapnia refractory to chronic NIV. In the group of patients able to complete the 24 hours treatment, the effect was retained for 48–96 hours after discontinuation of ECCO₂R.

The pathophysiological hallmark of COPD is the combination of the impairment of respiratory mechanics with the weakness of the inspiratory muscles. Under these circumstances, the patients reduce alveolar ventilation,¹ so that hypercapnia occurs.² Compensatory mechanisms such as bicarbonate production by body buffers keep pH in the physiological ranges stabilising the clinical manifestations of COPD and leading to chronic hypercapnia.⁷ In these patients, NIV has been shown to effectively improve outcome preventing acute exacerbation.⁸ However, chronic NIV may fail to decrease PaCO₂.^{4,5} We, therefore, challenged the hypothesis that ECCO₂R, may improve CO₂ clearance in patients with chronic hypercapnia unresponsive to NIV. Regardless of the expected reduction of PaCO₂ with ECCO₂R, we observed that values PaCO₂ remained lower than those observed at baseline after a relatively long period of time after ECCO₂R was interrupted. Interestingly the patients with higher forced expiratory volume in 1 s (n.3 and 5), returned to PaCO₂ baseline values later than those with more limited ventilator capacity, and this suggest, that this subset of patients, may better respond to ECCO₂R. Nevertheless our results might allow to propose the concept of ‘CO₂ dialysis’ in analogy with renal dialysis, using a ferula as venous access.

The mechanisms underlying this response are not clearly identified. However, it might be speculated that, since in the case of

chronic hypercapnia, tissues CO₂ store capacities able to stabilise CO₂ tension in the circulating blood are saturated,⁹ the observation that following interruption of extracorporeal support, PaCO₂ returned to baseline values in 48–96 hours may suggest that removing CO₂ through the extracorporeal circuit may empty parts of the CO₂ buffers. This empty space may therefore re-establish the CO₂ storing capacity allowing transient normocapnia during ‘unassisted’ breathing.

The proof-of-concept nature of this study is the major limitation. In fact, we focused exclusively to detect a signal whether ECCO₂R may provide, a time window ‘free’ from hypercapnia in patients. The study demonstrated however the feasibility of the hypothesis and therefore launch future investigations aimed to assess the ‘dose–response curve’ (how many hours of ECCO₂R are needed to provide the longest time window ‘free’ from hypercapnia) and selection of ideal inclusion/exclusion criteria. Further step will be tackle safety, the evidence of clinical benefits that include the reduction of occurrence of episodes of acute decompensation, the improvement of dyspnoea, exercise capacity and health-related quality of life. Finally, further research is needed in this area to get information about the sample size required for a larger trial.

In conclusion, this study shows that in patients with stable hypercapnic COPD not responding to home NIV, ECCO₂R lowers PaCO₂ that returned to baseline values in >48 hour after suspension. These data might allow to propose the concept of ‘CO₂ dialysis’ and support the need of further studies of CO₂ dialysis.

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REFERENCES

- 1 Tobin MJ, Laghi F, Brochard L. Role of the respiratory muscles in acute respiratory failure of COPD: lessons from weaning failure. *J Appl Physiol* 2009;107:962–70.
- 2 Hedsund C, Wilcke TR, Berg RMG. Defining “stable chronic hypercapnia” in patients with COPD: the physiological perspective. *Eur Respir J* 2020;55:1902172.
- 3 Ergon B, Oczkowski S, Rochweg B, et al. European respiratory Society guidelines on long-term home non-invasive ventilation for management of COPD. *Eur Respir J* 2019;54:1901003.
- 4 Köhnlein T, Windisch W, Köhler D, et al. Non-Invasive positive pressure ventilation for the treatment of severe stable chronic obstructive pulmonary disease: a prospective, multicentre, randomised, controlled clinical trial. *The Lancet Respiratory Medicine* 2014;2:698–705.
- 5 Moretti M, Cilione C, Tampieri A, et al. Incidence and causes of non-invasive mechanical ventilation failure after initial success. *Thorax* 2000;55:819–25.
- 6 Del Sorbo L, Pisani L, Filippini C, et al. Extracorporeal CO₂ removal in hypercapnic patients at risk of noninvasive ventilation failure: a matched cohort study with historical control. *Crit Care Med* 2015;43:120–7.
- 7 Schwartz WB, Brackett NC, Cohen JJ. The response of extracellular hydrogen ion concentration to graded degrees of chronic hypercapnia: the physiologic limits of the defense of pH. *J Clin Invest* 1965;44:291–301.
- 8 Murphy PB, Rehal S, Arbane G, et al. Effect of home noninvasive ventilation with oxygen therapy vs oxygen therapy alone on hospital readmission or death after an acute COPD exacerbation. *JAMA* 2017;317:2177–86.
- 9 Cherniack NS, Longobardo GS. Oxygen and carbon dioxide gas stores of the body. *Physiol Rev* 1970;50:196–243.