Extracorporeal CO_2 removal ($ECCO_2R$) in patients with stable COPD with chronic hypercapnia: a proof-of-concept study

Lara Pisani,[1] Stefano Nava,[1] Emilia Desiderio,[2] Mario Polverino,[2] Tommaso Tonetti ,[3] V Marco Ranieri[3]

[1]Department of Clinical, Integrated and Experimental Medicine (DIMES), Respiratory and Critical Care Unit, S. Orsola-Malpighi Hospital, Alma Mater Studiorum University of Bologna, Bologna, Emilia-Romagna, Italy
[2]Unità di Pneumologia,Dipartimento di Medicina, Scafati, Italy, Mauro Scarlato Hospital, Scafati, Campania, Italy
[3]Dipartimento di Scienze Mediche e Chirurgiche, Anesthesia and Critical Care Medicine,Policlinico di Sant'Orsola, Bologna, Italy, Alma Mater Studiorum University of Bologna, Bologna, Emilia-Romagna, Italy

Correspondence to
Professor Stefano Nava, Department of Clinical, Integrated and Experimental Medicine (DIMES), Respiratory and Critical Care Unit, S. Orsola-Malpighi Hospital, Alma Mater Studiorum University of Bologna, Bologna 40126, Italy; stefanava@gmail.com

Received 3 March 2020
Revised 26 May 2020
Accepted 26 May 2020

To cite: Pisani L, Nava S, Desiderio E, *et al*. *Thorax* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/thoraxjnl-2020-214744

Abstract Domiciliary non-invasive ventilation (NIV) effectively reduces arterial carbon dioxide pressure ($PaCO_2$) in patients with stable hypercapnic chronic obstructive pulmonary disease, but a consistent percentage of them may remain hypercapnic. We hypothesised that extracorporeal CO_2 removal ($ECCO_2R$) may lower their $PaCO_2$. Ten patients hypercapnic despite ≥6 months of NIV underwent a 24-hour trial of $ECCO_2R$. Six patients completed the $ECCO_2R$-trial with a $PaCO_2$ drop ranging between 23% and 47%. Time to return to baseline after interruption ranged 48–96 hours. In four patients, mechanical events led to $ECCO_2R$ premature interruption, despite a decreased in $PaCO_2$. This time window 'free' from hypercapnia might allow to propose the concept of 'CO_2 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 CO_2 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 CO_2 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 ($PaCO_2$) reduction.[4 5]

Extracorporeal CO_2 removal ($ECCO_2R$) may decrease $PaCO_2$ 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 $ECCO_2R$ may effectively and safely lower $PaCO_2$ 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 $PaCO_2$ >50 mm Hg with a pH >7.35. $ECCO_2R$ was proposed in patients enrolled in an home care NIV programme for at least 6 months, not responding in terms of $PaCO_2$ 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 cmH_20 and NIV average use was 5.8±1.1 hours/night. Patients were excluded if contraindication to $ECCO_2R$ were present[6] or if they had a body mass index >30 or confirmed sleep apnea syndrome.

Patients underwent a 24-hour trial of $ECCO_2R$ 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 m^2, 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 $ECCO_2R$ and every 6–8 hours after disconnection until daytime values of $PaCO_2$ returned at baseline level. Patients remained on spontaneous breathing until values of $PaCO_2$ returned to the levels at baseline. NIV was hence restored.

Potential adverse events were classified as mechanical and patient related[6] and daily assessed for 15 days after the $ECCO_2R$ trial. Occurrence of any adverse event during the $ECCO_2R$ trial led to treatment interruption and catheter removal.

RESULTS

$ECCO_2R$ was implemented in ten patients. Baseline characteristics of patients and $ECCO_2R$ settings are shown in table 1.

Twenty-four hours of $ECCO_2R$ were completed in six patients causing a reduction in $PaCO_2$ ranging between 23% and 47% (figure 1A). Following interruption of $ECCO_2R$, the time required to return to baseline values of $PaCO_2$ ranged between 48 and 96 hours (table 1). In four patients, mechanical related adverse event (circuit clotting, catheter displacement and pump malfunctioning) led to $ECCO_2R$ interruption (figure 1B) after 2–23 hours of treatment (table 1). Of note, values of $PaCO_2$ immediately before $ECCO_2R$ interruption were 23%–33% lower than $PaCO_2$ at baseline. Values of

Table 1 Baseline values

Patients	Baseline values								$ECCO_2R$ settings			
Completed $ECCO_2R$ trial	Gender	Age (years)	FEV_1 (% of predicted)	MMRC	Charlson Index	$PaCO_2$ (mm Hg)*	pH*	$HCO3^-$ (mmol)*	Blood Flow (mL/min)	Heparin (IU/kg)	aPTT ratio	Time to return to baseline values of $PaCO_2$ (hours)
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 $ECCO_2R$ trial												Reasons and time of $ECCO_2R$ 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; $ECCO_2R$, extracorporeal CO_2 removal; FEV_1, forced expiratory volume in 1s; $HCO3^-$, bicarbonate; MMRC, modified British Medical Research Council questionnaire; $PaCO_2$, partial arterial pressure of carbon dioxide.

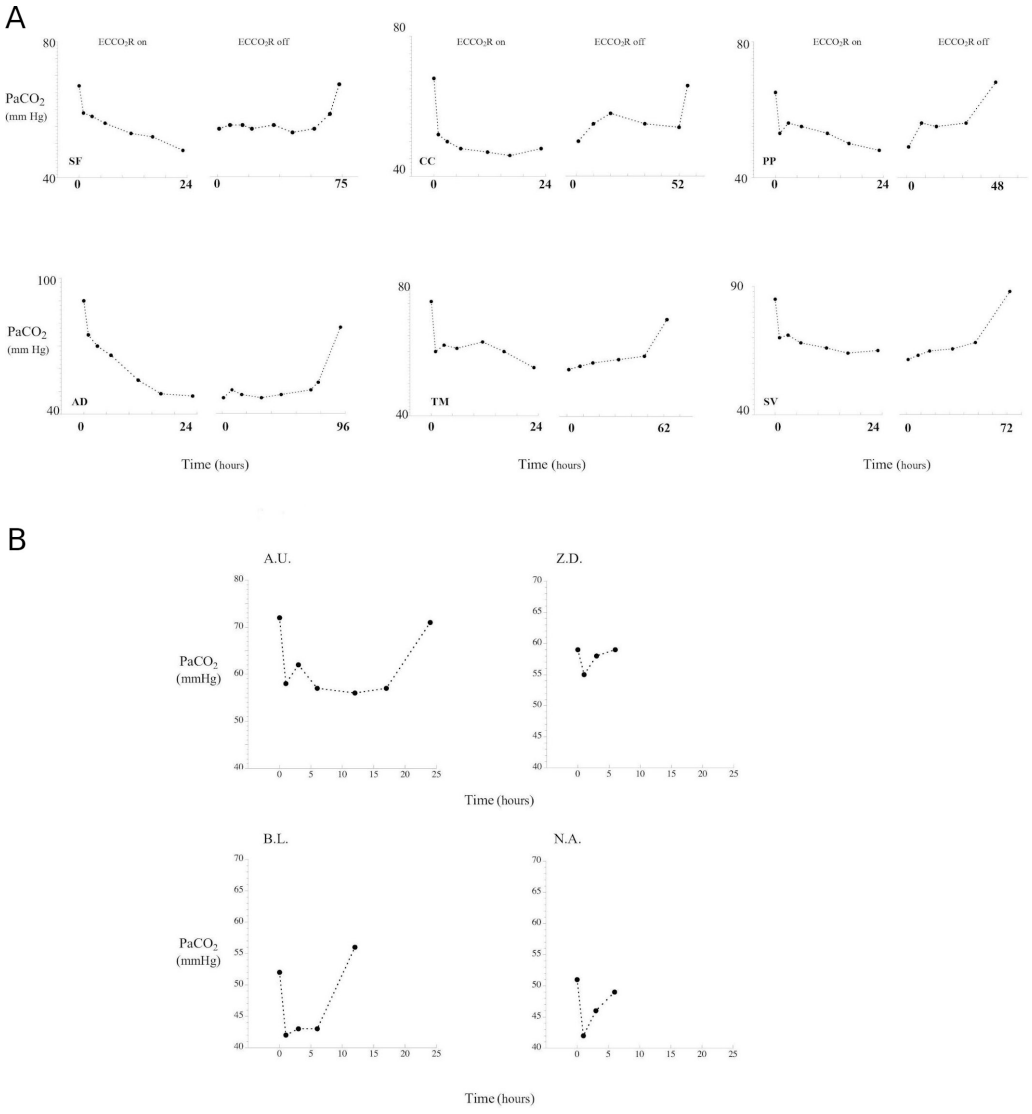

Figure 1 Individual levels of $PaCO_2$ during $ECCO_2R$ in all patients completing the study (PANEL A) or interrupting the trial for a technical problem (PANEL B). $ECCO_2R$, extracorporeal CO_2 removal; $PaCO_2$, arterial carbon dioxide pressure.

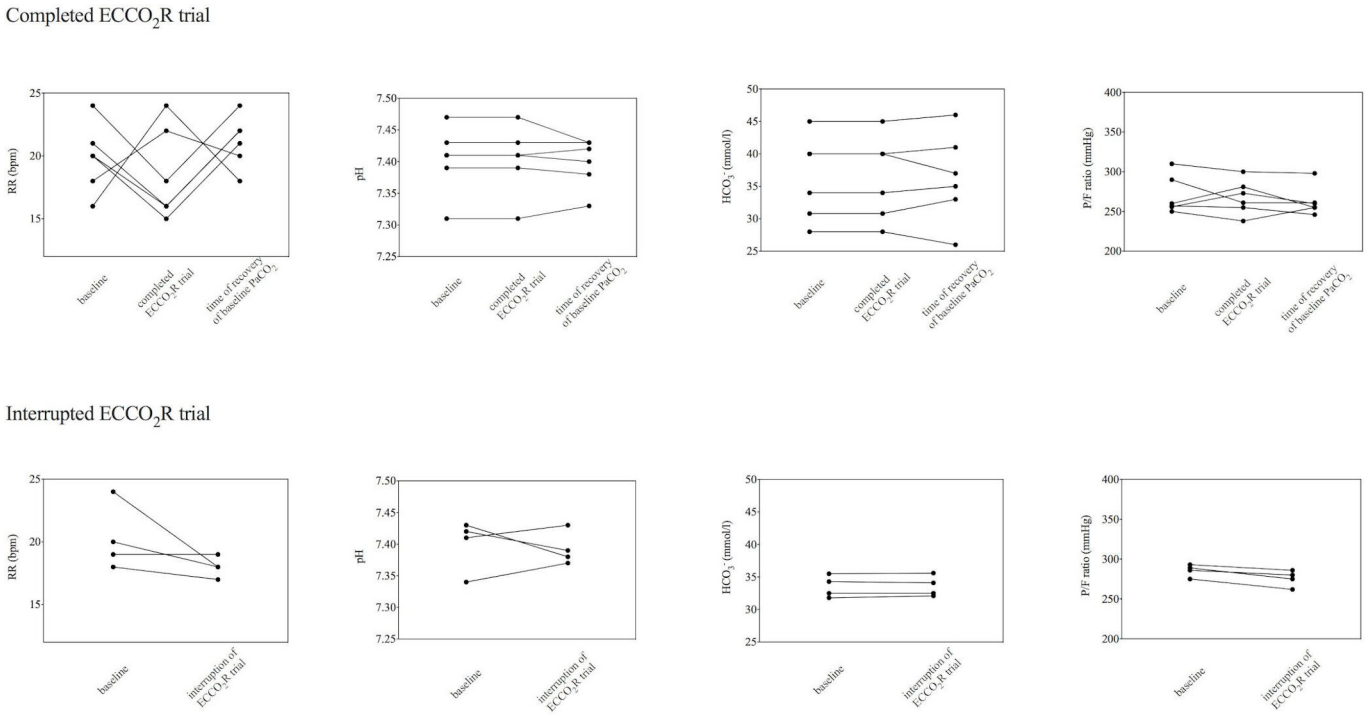

Figure 2 Individual values of pH, HCO3-, PaO_2/FiO_2 and respiratory rate, during $ECCO_2R$ in representative patients completing the study (upper part) or interrupting the trial for a technical problem (lower part). $ECCO_2R$, extracorporeal CO_2 removal; HCO_3-: bicarbonate; PaO_2/FiO_2, arterial oxygen tension/fractional inspired oxygen.

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

No patient-related adverse events[6] were observed for 15 days following $ECCO_2R$ trial.

DISCUSSION

This study shows that it is possible to safely lower $PaCO_2$ with $ECCO_2R$ 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 $ECCO_2R$.

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 $PaCO_2$.[4 5] We, therefore, challenged the hypothesis that $ECCO_2R$, may improve CO_2 clearance in patients with chronic hypercapnia unresponsive to NIV. Regardless of the expected reduction of $PaCO_2$ with $ECCO_2R$, we observed that values $PaCO_2$ remained lower than those observed at baseline after a relatively long period of time after $ECCO_2R$ was interrupted. Interestingly the patients with higher forced expiratory volume in 1 s (n.3 and 5), returned to $PaCO_2$ baseline values later than those with more limited ventilator capacity, and this suggest, that this subset of patients, may better respond to $ECCO_2R$. Nevertheless our results might allow to propose the concept of 'CO_2 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 CO_2 store capacities able to stabilise CO_2 tension in the circulating blood are saturated,[9] the observation that following interruption of extracorporeal support, $PaCO_2$ returned to baseline values in 48–96 hours may suggest that removing CO_2 through the extracorporeal circuit may empty parts of the CO_2 buffers. This empty space may therefore re-establish the CO_2 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 $ECCO_2R$ 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 $ECCO_2R$ 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, $ECCO_2R$ lowers $PaCO_2$ that returned to baseline values in >48 hour after suspension. These data might allow to propose the concept of 'CO_2 dialysis' and support the need of further studies of CO_2 dialysis.

Contributors LP performing the experimental trial—writing paper. SN study design, performing experimental trial, writing paper. ED performing the experimental trial. MP performing the experimental trial, revising paper. TT statistical analysis. VMR study design, writing paper.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval Review boards approved the protocol.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iD
Tommaso Tonetti http://orcid.org/0000-0001-9676-3595

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 Ergan B, Oczkowski S, Rochwerg 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.