



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

Funding

None.

References

- Murchu EO, Byrne P, Walsh KA, Carty PG, Connolly M, de Gascun C, et al. Immune response following infection with SARS-CoV-2 and other coronaviruses: a rapid review. *Rev Med Virol.* 2020. Available from: <https://onlinelibrary.wiley.com/doi/10.1002/rmv.2162>. [Accessed 7 November 2020].
- González-Castro A, Escudero-Acha P, Peñasco Y, Leizaola O, Martínez de Pinillos Sánchez V, García de Lorenzo A. Cuidados intensivos durante la epidemia de coronavirus 2019. *Med Intensiva.* 2020;44:351–62.
- Etridge AWD, Kaczorowska J, Hoste ACR, Bakker M, Klein M, Loens K, et al. Seasonal coronavirus protective immunity is short-lasting. *Nat Med.* 2020. Available from: <http://www.nature.com/articles/s41591-020-1083-1>. [Accessed 7 November 2020].
- Long Q-X, Tang X-J, Shi Q-L, Li Q, Deng H-J, Yuan J, et al. Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections. *Nat Med.* 2020;26:1200–4.
- To KK, Hung IF, Ip JD, Chu WH, Chan WM, Tam AR, et al. COVID-19 re-infection by a phylogenetically distinct SARS-coronavirus-2 strain confirmed by whole genome sequencing. *Clin Infect Dis.* 2020, <http://dx.doi.org/10.1093/cid/ciaa1275>.
- Seydoux E, Homad LJ, MacCamy AJ, Parks KR, Hurlburt NK, Jennewein MF, et al. Analysis of a SARS-CoV-2-infected individual reveals development of potent neutralizing antibodies with limited somatic mutation. *Immunity.* 2020;53, 98.e5–105.e5.
- Tillett RL, Sevinsky JR, Hartley PD, Kerwin H, Crawford N, Gorzalski A, et al. Genomic evidence for reinfection with SARS-CoV-2: a case study. *Lancet Infect Dis.* 2020. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S1473309920307647>. [Accessed 7 November 2020].
- Velikova TV, Kotsev SV, Georgiev DS, Batselova HM. Immunological aspects of COVID-19: what do we know? *World J Biol Chem.* 2020;11:14–29.
- Chandrashekar A, Liu J, Martinot AJ, McMahan K, Mercado NB, Peter L, et al. SARS-CoV-2 infection protects against rechallenge in rhesus macaques. *Science.* 2020;369:812–7.
- Overbaugh J. Understanding protection from SARS-CoV-2 by studying reinfection. *Nat Med.* 2020:1–2.
- To KKW, Hung IFN, Chan KH, Yuan S, To WK, Tsang DNC, et al. Serum antibody profile of a patient with coronavirus disease 2019 reinfection. *Clin Infect Dis.* 2020, <http://dx.doi.org/10.1093/cid/ciaa1368>.

I. Romera*, K. Núñez, M. Calizaya, I. Baeza, R. Molina, J. Morillas

Servicio de Medicina Intensiva, SCIAS Hospital de Barcelona, Barcelona, Spain

*Corresponding author.

E-mail address: irene.r.s@outlook.com (I. Romera).

2173-5727/ © 2021 Elsevier España, S.L.U. and SEMICYUC. All rights reserved.

Combination of airway pressure release ventilation with inverted inspiration-exhalation ratio and low-flow CO₂ removal devices with renal replacement therapy in refractory hypoxemia[☆]



Combinación de la ventilación con liberación de presión con la relación inspiración-espирación invertida y los dispositivos de eliminación de CO₂ de bajo flujo con terapia de sustitución renal en la hipoxemia refractaria

Dear Editor,

Acute respiratory failure which under pneumoprotective measures persistently maintains PaO₂/FiO₂ < 100 or a plateau P > 30 cmH₂O can be classified as refractory hypoxemia. The different therapeutic strategies under such circumstances include the combination of pressure-controlled ventilation and

the inverted inspiration-exhalation ratio (inverted I:E): airway pressure release ventilation (APRV).¹

We present a series of three cases of refractory hypoxemia in which APRV was applied in combination with a low-flow CO₂ removal device with renal replacement therapy (ECCO₂R-RRT). Table 1 details the clinical-epidemiological and evolutive characteristics of the three cases.

The first case in which both therapies were combined corresponded to a 75-year-old male admitted to the Intensive Care Unit (ICU) due to sepsis of respiratory origin. The patient developed severe acute respiratory distress syndrome (ARDS) secondary to nosocomial pneumonia, and mechanical ventilation was started. Anuric renal failure was diagnosed and renal replacement therapy (RRT) was decided. After 9 h of protective ventilation, and due to the persistence of refractory hypoxemia, we introduced APRV followed by ECCO₂R-RRT. The patient was discharged after 40 days in the ICU.

The second case corresponded to a patient admitted to the ICU with a diagnosis of possibly progressing multiple myeloma with established renal failure and severe respiratory failure secondary to community-acquired pneumonia. Upon admission to intensive care, mechanical ventilation was started and pneumoprotective measures were adopted, together with RRT. In view of the failure of these measures and the rapid progression of the clinical condition, combined therapy with APRV and ECCO₂R-RRT was started. Despite initial improvement, however, the patient died of hypoxia in the following 12 h.

The third case corresponded to an episode of respiratory failure of uncertain origin in a woman who had been treated with cetuximab due to a tumor of the floor of the mouth. She had undergone blood product transfusion 24 h before developing rapidly evolving severe ARDS. The patient was admitted to the ICU due to respiratory failure that progressed with multi-organ failure and anuric acute respiratory failure. In this case, ECCO₂R was started 24 h before switching the ventilatory mode

[☆] Please cite this article as: González-Castro A, Escudero Acha P, Rodríguez Borregán JC, Peñasco Y, Blanco Huelga C, Cuenca Fito E. Combinación de la ventilación con liberación de presión con la relación inspiración-espирación invertida y los dispositivos de eliminación de CO₂ de bajo flujo con terapia de sustitución renal en la hipoxemia refractaria. *Med Intensiva.* 2021;45:376–379.

Table 1 Clinical, epidemiological and evolutive parameters of the patients.

	Patient 1	Patient 2	Patient 3
Age (years)	75	41	61
Gender	Male	Male	Female
Comorbidities	Yes	Yes	Yes
Disease causing RF	ARDS due to sepsis (Kartagener syndrome)	Pneumonia (multiple myeloma)	TRALI vs. pneumonitis
<i>Pulmonary risk factors for ARDS</i>		Yes	Yes
CAP	No	Yes	No
Nosocomial pneumonia	Yes	No	No
Aspiration pneumonia	No	No	No
<i>Non-pulmonary risk factors for ARDS</i>			
Murray	3	3.25	3
Ventilatory mode before APRV-ECCO ₂ R	PRVC	VC	VC
<i>Adjuvant therapies before APRV ECCO₂R</i>			
Protective ventilation (VT =6 ml/kg)	Yes	Yes	Yes
Neuromuscular block	Yes	Yes	Yes
Prone position	Yes	Yes	Yes
Nitric oxide	No	No	No
Time from intubation to start of APRV ECCO ₂ R	9 h	6 h	24 h
<i>Reason for ending ECCO₂R</i>			
Treatment success	Yes	No	Yes
Death	No	Yes	No
<i>Follow-up</i>			
Recovery from severe ARDS	Yes	No	Yes
Days of mechanical ventilation	32	2	9
ICU stay	40	2	9
ICU outcome (alive/deceased)	Alive	Deceased	Deceased
Cause of death related to ARDS	–	Yes	No (AMI)

APRV: airway pressure release ventilation; ECCO₂R: extracorporeal carbon dioxide removal; AMI: acute myocardial infarction; RF: respiratory failure; CAP: community-acquired pneumonia; ARDS: acute respiratory distress syndrome; ICU: Intensive Care Unit; VC: volume control; PRVC: pressure-regulated volume control.

to APRV. On the eighth day of mechanical ventilation, and in view of resolution of the lung disease, mechanical ventilation weaning maneuvers were started. The patient died 24 h later due to acute myocardial infarction.

Table 2 details the modifications of the ventilatory parameters, ECCO₂R and the blood gas and hemodynamic values following the start of combined APRV and ECCO₂R-RRT.

The use of VV ECMO was contraindicated in all three cases due to the patient age and lung disease without predictable recovery (important bronchiectasis in Kartagener syndrome) in the first case, and comorbidities (active malignant disease) in the other two cases.²

Ventilatory management with APRV was carried out following the clinical guidelines of Habashi³ for the transition from conventional ventilation to APRV (P high = plateau).

In APRV, the ventilator is equipped with an active expiratory valve that allows spontaneous breathing of the patient in any of the pressure phases, and the duration of the “high pressure” phase is always longer than that of the “low pressure” phase – this being equivalent to an inverted I:E ratio.⁴

In relation to mechanical ventilation injury, Protti et al. found that, for a given total amount of strain, a higher static strain component (PEEP, air trapping) results in lesser lung injury than the use of dynamic strain.⁵

In theory, APRV allows the patient to spend most of the time in a situation of high static strain (P high) and low dynamic

strain; consequently, the risk of lung injury should decrease in comparison with the conventional modes that give rise to low static strain and high dynamic strain.⁶

However, caution is required when interpreting the effect of spontaneous breathing in APRV in the context of lung injury, since a number of factors intervene: the combination of spontaneous and mandatory respirations, adjustment of the ventilator, and the degree of lung injury. Neumann et al., on analyzing the possible adverse effects of APRV, found that spontaneous respiration could cause very high tidal volume (VT) and pleural pressure changes, which would be associated to high transpulmonary pressures and an increased risk of ventilator-induced lung injury (VILI).⁷ These aspects sometimes oblige an increase in patient sedation, or even the use of relaxation.

In our three scenarios, the combination of prior muscle relaxation with the consequent absence of spontaneous respiration, the decrease in functional lung parenchyma and the inverted I:E ratio in APRV appear to inevitably require the adoption of measures to counter the increase in PaCO₂ and control its harmful effects upon the lung, such as delayed alveolar repair after lung injury, decreased alveolar fluid reabsorption rates, and the inhibition of alveolar cell proliferation.⁸

An alternative in these situations is the use of carbon dioxide removers. In our case, and in view of the need for RRT due to different reasons, ECCO₂R-RRT was the treatment used.

Table 2 Evolution of the ventilatory, blood gas, ECCO₂R, hemodynamic and sedoanalgesia parameters during the first 24 hours.

	Patient 1					Patient 2					Patient 3				
	Basal	4 h	8 h	12 h	24 h	Basal	4 h	8 h	12 h	24 h	Basal	4 h	8 h	12 h	24 h
<i>Ventilatory parameters</i>															
T high (s)	4	4	4	4	4	5	5	5	5	–	4	6.5	6.5	6.5	6.5
P high (cmH ₂ O)	30	30	31	25	25	22	22	22	22	–	28	22	28	26	26
T low (s)	1	1	1	1	1	1.5	1.5	1.5	1.5	–	1	1	1	1	1
P low (cmH ₂ O)	5	5	5	2	2	1	1	1	1	–	2	2	2	2	2
Compliance	31	31	33	43	46	30.9	29	30.9	–	–	20	25	25	34	23
P/F	136	106	125	130	154	87	97	87	–	–	100	118	224	112	120
<i>Blood gas values</i>															
pH	7.22	7.2	7.28	7.31	7.4	7.16	7.2	7.16	7.1	–	7.39	7.34	7.38	7.39	7.42
PaO ₂ (mmHg)	95.3	74.6	87.5	78.5	77.3	48.5	65.8	67	67	–	49.8	45.7	101	56	67.2
PaCO ₂ (mmHg)	60.7	64.7	51.9	40.9	38.8	62.6	52.9	40	92	–	39.5	59.1	41	41	40.2
HCO ₃ (mmol/l)	24.1	24.1	23.7	20	23.5	21.5	19.9	13.6	20.7	–	23.8	24.4	23.2	24.7	25.3
Lactate (mmol/l)	0.7	0.6	0.7	0.9	0.8	0.9	0.9	0.8	1.5	–	2.7	2.3	2.2	2.4	2.3
<i>ECCO₂R parameters</i>															
Blood flow (ml/min)	450	450	450	450	450	280	400	300	350	–	400	400	400	400	400
Sweep gas flow (l/min)	0	10	10	10	10	0	10	10	10	–	15	15	15	15	15
<i>Hemodynamic parameters</i>															
MBP (mmHg)	84	75	97	95	80	65	75	80	55	–	70	75	65	60	70
HR (bpm)	106	92	79	70	73	110	90	80	100	–	55	60	60	65	50
Noradrenaline (μg/kg per min)	0	0.44	0	0	0	0.25	0.25	0.25	0.36	–	0.26	0.23	0.26	0.26	0.26
Dobutamine (μg/kg per min)	0	0	0	0	0	0	0	0	0	–	0	0	0	0	0
<i>Sedation and analgesia</i>															
Midazolam	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	–	Yes	Yes	Yes	Yes	Yes
Propofol	No	No	No	No	No	No	No	No	No	–	No	No	No	No	No
Fentanyl	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	–	Yes	Yes	Yes	Yes	Yes
Cisatracurium	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	–	Yes	Yes	Yes	Yes	Yes

ECCO₂R: extracorporeal carbon dioxide removal; HR: heart rate; MBP: mean blood pressure; P/F: PaO₂/FiO₂.

In our three patients, following the decision to start ECCO₂R-RRT, and after priming, the device was connected to the patient and the extracorporeal blood flow was progressively increased to 400 ml/min. The sweep gas flow across the membrane was kept at 0 l/min during this phase, as a result of which no CO₂ was initially removed.

Promising results have been documented with ECCO₂R-RRT in animals and in small studies involving patients with ARDS,⁹ and the technique requires no specific large-caliber venous accesses. Due to its low flow, this technology does not allow adequate extracorporeal oxygenation. However, a flow of 350–500 ml/min suffices to eliminate half of the production of CO₂; consequently, ECCO₂R is an interesting tool in such situations.^{7,10}

Financial support

The present study has received no funding of any kind.

Conflicts of interest

The authors declare that they have no conflicts of interest.

References

1. Delgado Martín M, Fernández Fernández R. Strategies against refractory hypoxemia in acute respiratory distress syndrome. *Med Intensiva*. 2013;37:423–30.
2. Fernández-Mondéjar E, Fuset-Cabanes MP, Grau-Carmona T, López-Sánchez M, Peñuelas Ó, Pérez-Vela JL, et al. The use of ECMO in ICU. Recommendations of the Spanish Society of Critical Care Medicine and Coronary Units. *Med Intensiva*. 2019;43:108–20.
3. Habashi NM. Other approaches to open-lung ventilation: airway pressure release ventilation. *Crit Care Med*. 2005;33:S228–40.
4. Kuhlen R, Rossaint R. The role of spontaneous breathing during mechanical ventilation. *Respir Care*. 2002;47:296–330.
5. Protti A, Andreis DT, Monti M, Santini A, Sparacino CC, Langer T, et al. Lung stress and strain during mechanical ventilation: any difference between statics and dynamics? *Crit Care Med*. 2013;41:1046–55.
6. Mireles-Cabodevila E, Dugar S, Chatburn RL. APRV for ARDS: the complexities of a mode and how it affects even the best trials. *J Thorac Dis*. 2018;10:S1058–63.
7. Neumann P, Golisch W, Strohmeyer A, Buscher H, Burchardi H, Sydow M. Influence of different release times on spontaneous breathing pattern during airway pressure release ventilation. *Intensive Care Med*. 2002;28:1742–9.
8. Morales Quinteros L, Bringué Roque J, Kaufman D, Artigas Raventós A. Importance of carbon dioxide in the critical patient: implications at the cellular and clinical levels. *Med Intensiva*. 2019;43:234–42.

9. Schmidt M, Jaber S, Zogheib E, Godet T, Capellier G, Combes A. Feasibility and safety of low-flow extracorporeal CO₂ removal managed with a renal replacement platform to enhance lung-protective ventilation of patients with mild-to-moderate ARDS. *Crit Care*. 2018;22:122.
10. Winiszewski H, Aptel F, Belon F, Belin N, Chaignat C, Patry C, et al. Daily use of extracorporeal CO₂ removal in a critical care unit: indications and results. *J Intensive Care*. 2018;6:36.

A. González-Castro*, P. Escudero Acha, J.C. Rodríguez Borregán, Y. Peñasco, C. Blanco Huelga, E. Cuenca Fito

Servicio de Medicina Intensiva, Hospital Universitario Marqués de Valdecilla, Santander, Spain

*Corresponding author.

E-mail address: e409@humv.es (A. González-Castro).

2173-5727/ © 2021 Published by Elsevier España, S.L.U.

When success means focusing on the oxygen delivery. A case of conventional management of severe hypoxemia in SARS-CoV-2



Cuando el tratamiento adecuado consiste en evaluar el aporte de oxígeno. Manejo convencional de la hipoxemia severa en un paciente con SARS-CoV-2

Dear Editor:

SARS-CoV-2 challenged ICU doctors' ability to support patients with acute respiratory insufficiency. This was due to both the unexpectedly high rate of admissions and the severity of these patients. Through this case we would like to highlight the physiology guided management of a patient with profound hypoxemia. In spite of an apparently life threatening condition this patient had a good course with conventional management guided by invasive hemodynamic monitoring.

A 46 years old male was admitted to the ICU with presumptive diagnosis of SARS-CoV-2. Respiratory symptoms had started 10 days before admission to the emergency room. Due to hypoxemia and tachypnea as well as an X-ray with bilateral infiltrates, the patient was early transferred to ICU. Support with high flow oxygen was started but escalation to invasive mechanical ventilation (MV) was required due to persistent hypoxemia. Due to a PaO₂ = 60 mmHg despite FiO₂ 1 (with protective mechanical ventilation settings PEEP 10 cmH₂O, tidal volume 6 ml/kg, plateau pressure 20 cmH₂O) the patient was subjected to prone positioning therapy. The patient showed no change in respiratory mechanics during prone positioning but a slight improvement in oxygenation was observed. He completed a 16 h prone therapy session. Once in supine, oxygenation was severely deteriorated again with a PaO₂/FiO₂ < 80 mmHg hence extracorporeal membrane oxygenation (ECMO) therapy was proposed.¹ Additionally, he underwent invasive monitoring with a Swan-Ganz catheter. The patient showed moderate pulmonary hypertension (PASP 45 mmHg, PVRi 388 dyn s cm⁵), cardiac index 3.5 l min⁻¹ m² and a preserved mixed blood oxygen saturation around 75%. These data were complemented with a transthoracic echocardiogram that showed no right ventricular (RV) dysfunction (which was concordant with a pulmonary artery pulsatility index = 1.7), preserved left ventricular function and no signs of hypovolemia. Based on the preserved RV function and an adequate oxygen delivery with protective MV settings the decision of starting ECMO was postponed. Prone positioning sessions were continued up to a number of 5 and during the following days

both the patient's lung function (which was more prominent in prone) as well as pulmonary hemodynamics progressively improved. The patient was extubated 2 weeks later.

During times of health services overwhelming, the selection of patients who will benefit from therapies related with a high consumption of resources should be carefully and efficiently performed. In the ICU one of these therapies is ECMO. There are doubts about the long term prognosis of patients with SARS-CoV-2 who develop severe hypoxemia despite the gentlest MV. Besides this, the physiology of the patient with SARS-CoV-2 has been proposed to be different from typical ARDS²: (1) A high proportion of them have good compliance (Gattinoni's phenotype L) and in consequence management with low PEEP is recommended and (2) they show a blunted pulmonary vasoconstriction. Also, at least in our experience a low rate of systemic hemodynamic involvement is seen. Such differences could affect the indications of ECMO in these patients.³

Respiratory ECMO is indicated to ensure oxygen delivery in patients in whom this cannot be reached under protective MV settings.⁴ Other indications or goals are at least doubtful. Following this reasoning, comparing with typical ARDS, for the same arterial oxygen content, probably a lower proportion of SARS-CoV-2 patients would be subsidiaries of ECMO. A high compliance in a patient managed with relatively low PEEP could make it easier to reach safe settings including low plateau pressure, low driving pressure and tidal volume around 6 ml/kg⁵. If we put this altogether with the decreased pulmonary vascular response to hypoxia, a low prevalence of RV failure could be expected. Finally, in the absence of RV dysfunction, patients with preserved left ventricle function can maintain a cardiac output enough to keep an adequate oxygen delivery. Therefore, deciding starting ECMO based only on PaO₂ may not be adequate to cover the entire physiologic process in some patients with severe respiratory insufficiency in the context of COVID-19. This resolution should be adjusted to the current recommendations regarding the availability of resources.⁶

Another important finding of this case is the apparently low O₂ extraction which could be compatible with low systemic involvement at least at the disease stage at which the patient was. Also this could be due to the adequate sedation and the use neuromuscular blockade. In this context we would like to highlight that oxygen delivery depends essentially on cardiac output, hemoglobin concentration and SaO₂. Therefore in patients without risk of low cardiac output, taking into account SaO₂/FiO₂ instead of PaO₂/FiO₂ could be a better index when taking the decision of escalating toward therapies such as ECMO.

Finally, we would like to remark that despite the severity of the hypoxemia in this patient, he did improve with conventional therapies. Moreover, in spite of the doubts regarding the usefulness of prone positioning in the presence of good