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REVIEW

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# Extracorporeal gas exchange for acute respiratory failure in adult patients: a systematic review

Matthieu Schmidt<sup>1</sup>, Carol Hodgson<sup>2</sup> and Alain Combes<sup>1\*</sup>

## Abstract

This article is one of ten reviews selected from the Annual Update in Intensive Care and Emergency Medicine 2015 and co-published as a series in *Critical Care*. Other articles in the series can be found online at <http://ccforum.com/series/annualupdate2015>. Further information about the Annual Update in Intensive Care and Emergency Medicine is available from <http://www.springer.com/series/8901>.

## Introduction

Mechanical ventilation remains the cornerstone of respiratory support for patients with acute respiratory failure. However, high pressure and volume associated with tidal ventilation are known to aggravate lung injury in this setting [1]. Furthermore, profound gas-exchange abnormalities threatening patients' lives can occur in the most severe forms of the disease despite recourse to conventional salvage therapies [2,3]. Extracorporeal gas exchange devices, i.e., venovenous extracorporeal membrane oxygenation (ECMO) and extracorporeal carbon dioxide removal (ECCO<sub>2</sub>R), were developed more than 40 years ago [4,5] to rescue these dying patients. Whereas venovenous ECMO provides complete extracorporeal blood oxygenation and decarboxylation using high blood flows (4–6 l/min) and large (20–30 Fr) cannulas [6–9], efficient extracorporeal CO<sub>2</sub> removal (with minimal blood oxygenation) can be achieved with ECCO<sub>2</sub>R devices using limited extracorporeal blood flow (0.4–1 l/min) and thin double lumen venous catheters (14–18 Fr) [10,11], because CO<sub>2</sub> clearance is more effective than oxygenation due to the greater solubility and more rapid diffusion of CO<sub>2</sub> [12]. Extracorporeal gas exchange devices also permit 'ultraprotective' mechanical ventilation with further

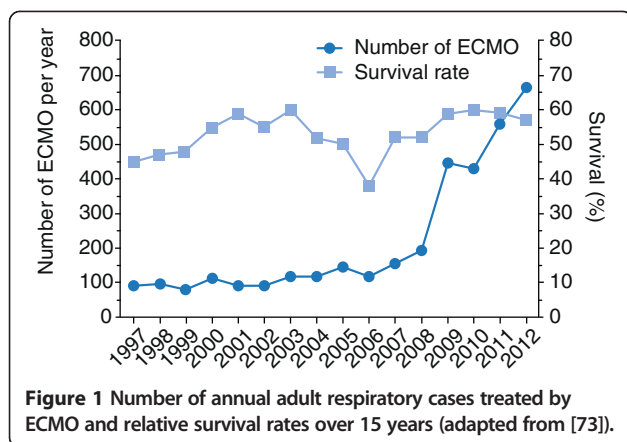
reduction of volume and pressure, which may ultimately enhance lung protection and improve clinical outcomes for patients with acute respiratory distress syndrome (ARDS). However, results of trials evaluating extracorporeal gas exchange for respiratory failure performed in the 1970s, 80s and 90s were often disappointing [13,14]. In recent years, major technological advances have occurred and the latest generation extracorporeal gas exchange devices, with polymethylpentene hollow-fiber membrane lungs and Mendler-designed centrifugal pumps offer lower resistance to blood flow, have smaller priming volumes, higher effective gas exchange properties and are coated with more biocompatible materials.

The successful use of ECMO for the most severe ARDS cases associated with the recent influenza A (H1N1) pandemic, in whom conventional ventilation was not successful [15–17], and positive results of the randomized Conventional ventilatory support versus Extracorporeal membrane oxygenation for Severe Adult Respiratory failure (CESAR) trial [18] have been associated with a steep increase in the number of VV-ECMO procedures performed in very recent years (Figure 1). In addition, a proof-of-concept study suggested that the very low tidal volume ventilation (3.5–5 ml/kg of predicted body weight) permitted by ECCO<sub>2</sub>R can improve pulmonary protection and decrease pulmonary inflammation in ARDS patients [19] and a recent randomized trial suggested that this strategy may be associated with better outcomes for moderate to severe ARDS patients [11].

The aim of this systematic review was to analyze studies reporting indications, associated complications and short- and long-term outcomes of extracorporeal gas exchange in adult patients with acute respiratory failure. It may ultimately help critical care physicians and researchers select better candidates for extracorporeal gas exchange and to design future observational and randomized clinical trials to evaluate these techniques.

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**Figure 1** Number of annual adult respiratory cases treated by ECMO and relative survival rates over 15 years (adapted from [73]).

## Methods

To achieve a high standard of reporting, we adopted Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [20,21].

### Search strategy

The detailed search strategy (identification, screening, eligibility and inclusion process) used to identify relevant studies is summarized in Figure 2. We used a detailed PubMed/MEDLINE, EMBASE and CINAHL query to identify randomized controlled trials (RCTs), controlled observational studies (retrospective and prospective) and case series with >5 patients who received extracorporeal gas exchange. Additionally, reference lists from relevant reviews, observational studies and clinical trials were hand-searched. Neonatal and pediatric studies (patients < 18 years of age) were excluded. Language of publication was limited to English and no restriction on the time was set on the primary literature searches. The query was last updated in June 2014.

### Study selection

Two independent researchers (MS and AC) conducted a two-step literature search. Studies were included according to the following criteria: 1) original study published in a peer-reviewed journal; and 2) analyzed/reported the use of extracorporeal gas exchange (i.e., ECMO or pumpless extracorporeal lung assist or extracorporeal CO<sub>2</sub> removal) and its specific outcomes for acute respiratory failure in adult patients. Any discrepancies between the two reviewers who examined the titles and abstracts of all relevant citations were resolved by discussion.

### Data extraction, quality assessment and analysis

The two reviewers (MS and AC) independently read the entire texts of the retrieved reports and rated study quality using well-established criteria [21,22]. RCT quality was graded using a nine-point scale combining elements from

Jadad's [21] and Chalmers' [23,24] scales, whereas the quality of case-controlled studies was appraised using the Newcastle-Ottawa scale [25]. In addition, both reviewers extracted the following data: First author, year of publication, country, study design, number of patients, demographic data, pre-ECMO ventilation and blood gas data and outcomes. Because of very high heterogeneity between studies, related to different generation ECMO and ECCO<sub>2</sub>R devices used in the last 40 years, different patient populations evaluated, and the scarcity of randomized or quasi-randomized trials (most of which were flawed by major methodological limitations) performed with the latest generation extracorporeal gas exchange techniques, we did not perform meta-analyses of randomized or quasi-randomized trials and choose to report and discuss only crude study results.

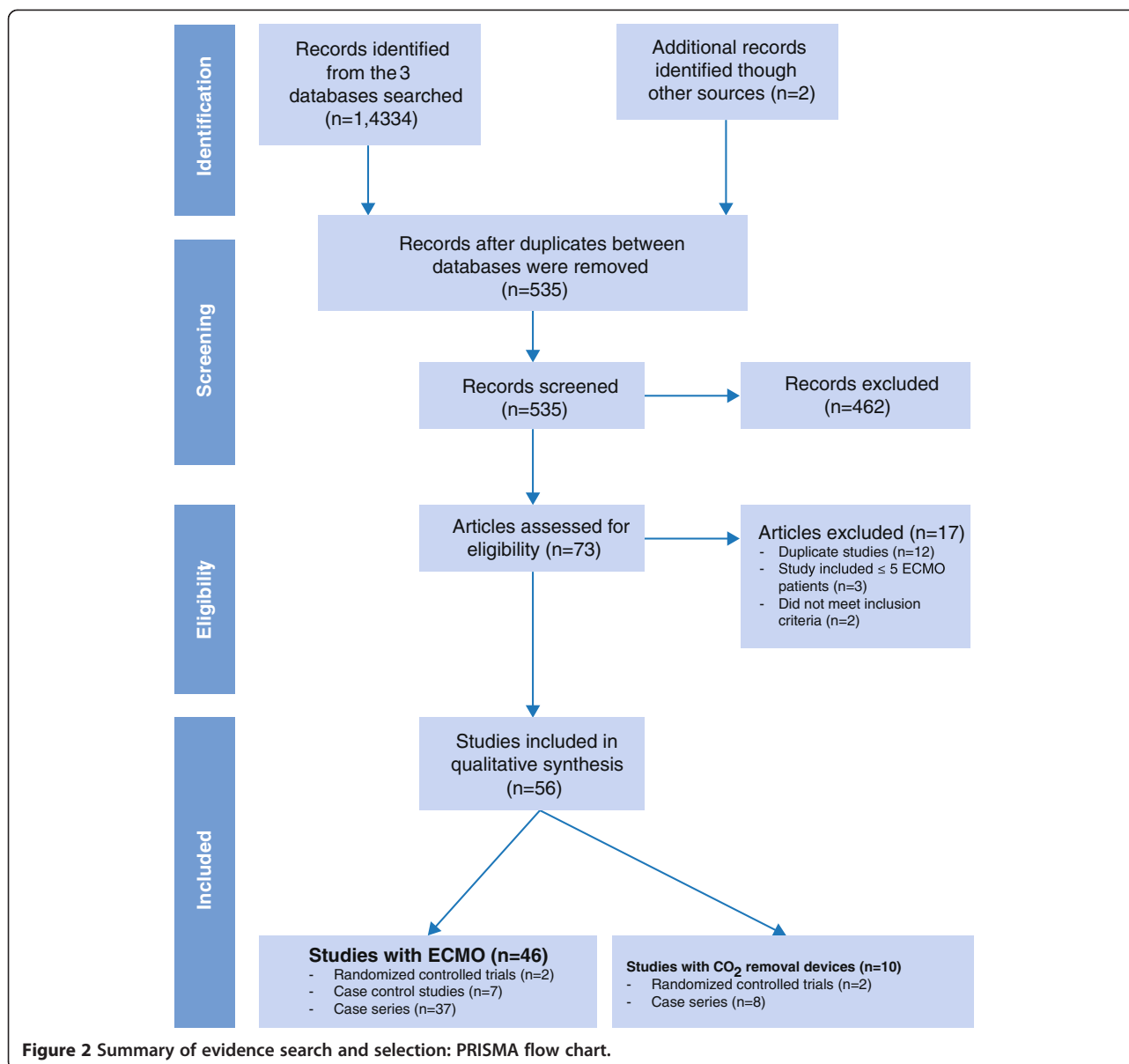
## Results

### Number of studies selected

The initial search yielded 535 articles, of which 462 were excluded through title and abstract review, leaving 73 articles potentially meeting our inclusion criteria. After a complete analysis of these, 17 articles were excluded. Of the remaining 56 studies that were evaluated, 4 were RCTs, 7 case-control studies, and 45 case series (Figure 2 and Tables 1, 2, 3, 4, 5 and 6). With the exception of two studies [13,18], all ECMO cohorts had an observational design. Sixteen studies reported on the outcomes of ARDS cases associated with the recent influenza A(H1N1) pandemic (Tables 4 and 5). Ten studies (2 randomized) reporting on ECCO<sub>2</sub>R devices in ARDS patients were retained for the review (Table 6). Overall study validity was adequate, with an average score of 8.1/9.0 on the Newcastle-Ottawa scale appraising the quality of case-control studies.

### ECMO and ARDS: studies of historical interest

In 1968, Kolobow et al. developed the first membrane oxygenator for long-term extracorporeal oxygenation [5]. Three years later, Donald Hill and colleagues described the first use of an ECMO device for acute respiratory failure in humans [4]. They reported on a 24-year-old polytrauma patient, who survived after 75 hours of veno-arterial ECMO. In cohort studies published up to the mid-2000s, the oldest ECMO technology combining roller pump, silicone membrane oxygenator and blood reservoir was used. Survival was 50% in a cohort of 1,473 patients (1986 to 2006, mean age 34 years, 78% had VV-ECMO) from the Extracorporeal Life Support Organization (ELSO) registry [26]. In that report, survival was comparable across study periods, although age and severity of disease were significantly higher for the most recent patients. Similarly, Hemmila et al. from Michigan University reported a survival of 52% in 255 adult patients



treated with ECMO between 1989 and 2003 [27]. Other case–control studies reported similar survival rates for patients treated with ECMO [28,29]. Interestingly, in a cohort of 150 patients with ARDS (mean age 42 years, mean SAPS II 45), of whom 32 received ECMO as a rescue therapy, ECMO support was not independently associated with a higher mortality [30].

#### ECMO and ARDS: results of randomized controlled trials

Over the last 30 years, only two RCTs of ECMO for ARDS patients have been conducted [13,18]. The National Institutes of Health (NIH) performed the first multicenter trial in the 1970s, enrolling 90 patients with severe ARDS refractory to conventional ventilation [13], of whom 42 received ECMO. Survival was extremely low (<10%) and

not different between groups. However, that study suffered from major methodological limitations. For example, the mode of ECMO support was only veno-arterial and when no improvement was observed after 5 days, ECMO was removed, which precluded the possibility of late clinical improvement. Because the ECMO group did not receive lung-protective ventilation, severe complications related to barotrauma occurred and since ECMO circuitry was not heparin-coated at that time, a very high percentage of patients had severe hemorrhagic complications due to excessive anticoagulation.

The most recent trial (CESAR), which was conducted in the UK from 2001 to 2006, evaluated a strategy of transfer to a single center (Glenfield, Leicester) that had ECMO capability while the patients randomized to the

**Table 1 Large, recent studies of ECMO for acute respiratory failure: Key patient features**

First author [ref]	Design	Prospective	Setting	Quality assessment <sup>§</sup>	Follow up	ECMO patients	Years	Age	Pneumonia, %	Mobile ECMO team, %	SOFA score
Peek, ECMO Arm, CESAR trial [18]	RCT	Y	Multi	RCT6	6 months	68	2001–2006	40 ± 13	62	0	–
Schmidt [50]	Case series	Y	Multi	–	Hospital discharge	2,355	2000–2012	41 (28–54)	34	–	–
Brogan [26]	Case series	N	Multi	–	Hospital discharge	1,473	1986–2006	35 (22–53)	26	–	–
Enger [51]	Case series	Y	Single	–	Hospital discharge	284	2008–2013	46 (43–48) <sup>†</sup>	49	47	11 (11–12)
Hemmila [27]	Case series	N	Single	–	Hospital discharge	280	1989–2003	38 ± 13	31	37	–
Schmid [32]	Case series	N	Single	–	ICU discharge	176	2007–2010	48 ± 17	58	34	12 ± 4
Schmidt [33]	Case series	N	Multi	–	6 months	140	2008–2012	44 (30–56)	71 <sup>£</sup>	68	12 (10–15)
Lindskov [31]	Case series	Y	Single	–	ICU discharge	124	1977–2011	42 (16–67)	64	85	–
Roch [49]	Case series	N	Single	–	Hospital discharge	85	2009–2013	47 ± 15	86	100	9 (7–11)
Rega [74]	Case series	N	Single	–	90 days	70	1997–2005	43 ± 18	41	–	–
Mols [28]	Case–control	Y	Single	7	Hospital discharge	62	1991–1999	35 ± 11	58	0	7 (6–9)
Muller [35]	Case series	Y	Single	–	ICU discharge	60	2006–2008	53 (21–78)	42	17	14 (11–16)
Lewandowski [29]	Case–control	Y	Single	9	ICU discharge	49	1989–1995	31 ± 14	37	–	–
Forrest [34]	Case series	N	Multi	–	Hospital discharge	38	2007–2010	34 (26–42)	89 <sup>#</sup>	100	8 (5–10)
Frenckner [75]	Case series	N	Single	–	ICU	38	1995–2002	38 (17–61)	60	32	–
Michaels [46]	Case series	N	Single	–	ICU discharge	36	2009–2012	40 ± 6	58 <sup>§</sup>	69	–
Beiderlinden [30]	Case–control	Y	Single	9	Hospital discharge	32	1998–2003	42 ± 13	53	–	14 ± 3

ICU, intensive care unit; Multi, multicenter; N, no; RCT, randomized control trial; SOFA; Sequential Organ Failure Assessment; Y, yes.

Data are given as mean ± SD or median (interquartile range). <sup>£</sup>26% were H1N1 pneumonia; <sup>#</sup>42% were H1N1 pneumonia; <sup>§</sup>44% were H1N1 pneumonia.

<sup>§</sup>Randomized controlled trial quality was graded using a nine-point scale combining elements from Jadad's [21] and Chalmers' scales [23,24] whereas the validity of case-controlled studies was appraised with the Newcastle-Ottawa scale [25]; <sup>†</sup>in the survivors.

**Table 2 Large, recent studies of ECMO for acute respiratory failure: Key pre-ECMO data and outcomes**

First author [ref]	PaO <sub>2</sub> /FiO <sub>2</sub>	pH	Plateau pressure	PEEP	LIS	Delay MV – ECMO, hours	Rescue therapies, %	Duration of ECMO, days	Hemorrhage, %	Intracerebral hemorrhage, %	Mortality, n (%)
Peek, ECMO Arm, CESAR trial [18]	76 ± 29	7.1 ± 0.1	–	14 ± 9	3.5 ± 0.6	36 (17–104)	–	10 (5–23)	–	0	33 (37%)
Schmidt [50]	59 (48–75)	7.25 (7.15–7.35)	36 (31–43)*	13 (10–16)	–	57 (19–151)	30	7 (4–13)	–	–	1,017 (43%)
Brogan [26]	57 (45–71)	7.27 (7.18–7.36)	40 (35–48)*	13 (10–16)	–	52 (20–160)	–	23 ± 20	30	4	732 (50%)
Enger [51]	69 (65–74) <sup>†</sup>	7.22 (7.22–7.25) <sup>†</sup>	35 (34–36) <sup>†</sup>	16 (16–17) <sup>†</sup>	3.5 (3.4–3.5) <sup>†</sup>	120 (96–168) <sup>†</sup>	–	10 (9–11) <sup>†</sup>	–	–	117 (41%)
Hemmila [27]	55 ± 16	7.31 ± 0.12	44 ± 11*	13 ± 5	–	96 ± 72	–	9 ± 8	–	3	123 (48%)
Schmid [32]	77 ± 47	7.2 ± 0.2	35 ± 6*	18 ± 6	3.4 ± 0.5	144 ± 240	–	12 ± 9	–	–	78 (44%)
Schmidt [33]	53(43–60)	7.22(7.15–7.32)	32 (30–35)	10 (8–12)	–	120 (24–264)	94	15 (8–30)	46	3	50 (36%)
Lindskov [31]	48 (37–60)	7.26 ± 0.15	37 (35–41)	–	–	–	–	9 (1–23)	–	9	36 (29%)
Roch [49]	60 (50–70)	7.1 ± 0.2	32 (29–35)	–	3.5 (3.3–3.7)	48 (24– 194)	85	9 (7–13)	29	2	48 (56%)
Rega [74]	56 ± 18	7.22 ± 0.18	44 ± 11*	13 ± 3	–	108 ± 178	–	7 ± 5	20	–	40 (57%)
Mols [28]	96 ± 51	7.30 (7.22–7.40)	–	–	3.2 ± 0.4	–	–	12 ± 7	7	2	28 (45%)
Muller [35]	64 (48–86)	7.20 (7.13–7.30)	36 (32–40)*	16 (13–20)	3.6 (3.3–3.8)	1.0 (1.0–4.8)	–	9 (5–13)	30	–	33 (55%)
Lewandowski [29]	–	7.32 ± 0.10	39 ± 7*	12 ± 3	3.4 ± 0.2	312 ± 216	–	23 ± 17	–	–	22 (45%)
Forrest [34]	57 (47–65)	7.20 (7.13–7.3)	–	16 (12–18)	3.7 (3.5–3.7)	48 (24–48)	34	10 (7–17)	37	3	5 (13%)
Frenckner [75]	47 (31–65)	–	41 (29–54)*	13 (0–20)	3.5 (3.0–4.0)	120 (24–672)	100	17 (2–57)	16	8	13 (34%)
Michaels [46]	52 ± 3	–	–	–	–	68 ± 9	–	7 ± 1	–	6	15 (40%)
Beiderlinden [30]	63 ± 28	7.1 ± 0.2	–	19 ± 3	3.8 ± 0.3	132 ± 168	–	10 (7–15)	–	–	15 (47%)

LIS, lung injury score; MV, mechanical ventilation; PEEP, positive end-expiratory pressure.

Data are given as mean ± SD or median (interquartile range). \*Peak pressure; <sup>†</sup>in the survivors.

**Table 3 Studies of ECMO for ARDS published before 1997 or including < 30 patients**

First author [ref]	Design	Prospective	Setting	Follow up	Quality of the study	ECMO patients	Years	Age, years	Pre ECMO PaO <sub>2</sub> /FiO <sub>2</sub> , mmHg	Length of ECMO, days	Mortality, n (%)
Zapol [13]	RCT	Y	Multi	ICU discharge	RCT4	42	1979	12 to 65	<83	<5 days	39 (92%)
Macha [76]	Case series	N	Single	Hospital discharge	–	33	1990–1995	36 ± 2	59 ± 5	6 ± 1	13 (39%)
Cordell-Smith [77]	Case series	N	Single	ICU discharge	–	28	1992–2000	27*	62*	6*	8 (29%)
Haneya [78]	Case series	Y	Single	ICU discharge	–	22	2010–2011	47 (36–61)	60 (46–75)	13 (8–19)	7 (32%)
Hodgson [66]	Case series	N	Single	8 months	–	21 <sup>£</sup>	2009–2011	36 ± 12	69(50–105)	11 (4–16)	3 (14%)
Huang [79]	Case series	N	Single	ICU discharge	–	16	2003–2005	32 ± 22	54 ± 8	7 ± 4	6 (37%)
Isgrò [80]	Case series	Y	Single	Hospital discharge	–	12	2004–2009	35 ± 19	60 ± 11	–	6 (54%)
Oshima [81]	Case series	N	Single	ICU discharge	–	11	2003–2008	52 ± 24	90 ± 10	10 ± 9	5 (45%)
Bermudez [82]	Case series	N	Single	ICU discharge	–	11	2009–2010	34 (25–54)	45 (28–248)	3 (0–11)	5 (45%)
Goulon [83]	Case series	N	Single	8 months	–	11	1973–1976	29 (22–37)	39 ± 12	3 (1–4)	9 (82%)
Park [84]	Case series	N	Multi	60 days	–	10	2011	47 (14–71)	50 (36–56)	5 (3–32)	6 (60%)
Park [85]	Case series	N	Single	ICU discharge	–	9	2008–2011	56 (51–64)	57 ± 8	12 ± 6	10 (55%)
Huang [79]	Case series	N	Single	11 (8–51) months	–	9	2004–2007	35 ± 10	49 (31–64)	6 (3–19)	7 (78%)
Rossaint [86]	Case series	N	Single	Hospital discharge	–	8	1993–1995	35 (24–49)	43 ± 4	8 ± 9	2 (25%)

ICU: intensive care unit; Multi: multicenter; N: no; RCT: randomized controlled trial; Y: yes.  
Data are given as mean ± SD or median (interquartile range). \*Mean; £ 55% were H1N1pneumonia.

**Table 4 Large studies of ECMO for H1N1-induced ARDS**

	Pham [17]	Noah [16]	Davies [15]	Patroniti [48]	Schmidt [33]	Michaels [46]	Takeda [43]	Holzgraefe [40]
Patients, n	123 <sup>5</sup>	69 <sup>£</sup>	68	49	36	15	14	13
Number of centers	33	4	15	14	3	1	12	1
Study design	Case control	Case control	Case control	Case series	Case series	Case series	Case series	Case series
Newcastle-Ottawa scale	9	8	8	7	–	–	–	–
Age, years	42 (32–53)	34 (28–46)	36 (27–45)	39 (32–46)	39 (28–53)	34 ± 4	54 (43–60)	31 (25–50)
BMI, kg/m <sup>2</sup>	30.5 ± 8.0	–	29 (23–36)	27 (24–35)	29 (25–36)	–	–	35 (31–42)
Pregnant or postpartum, n (%)	18 (15)	10 (17)	10 (16)	4 (8)	7 (19)	1(7)	1 (7)	3 (23)
SOFA	9.5 ± 4.0	9 (7–10)	–	7 (6–9)	11 (9–14)	–	16 (12–19)	–
Interval MV-ECMO, d	2 (1–5)	4 (2–7)	2 (1–5)	2 (1–5)	2 (0–5)	3.5 ± 0.8	5.0 (0.8–8.5)	1 (0–7)
Pre-ECMO parameters								
pH	7.26 ± 0.12	–	7.20 (7.10–7.30)	7.30 (7.22–7.40)	7.22 (7.15–7.32)	–	–	7.30(7.30–7.40)
PaO <sub>2</sub> /FiO <sub>2</sub> , mmHg	59 (51–71)	55 (46–63)	56 (48–63)	63 (56–79)	50 (41–55)	62 ± 6	50 (40–55)	52 (38–60)
Plateau pressure, mmHg	32 (29–35)	–	36 (33–38)	33 (30–35)	32 (30–35)	–	30 (29–35)	37 (31–38)
Lung injury score	3.5 (3.0–4.0)	3.5 (3.5–3.7)	3.8 (3.5–4.0)	3.8 (3.3–3.8)	–	–	–	3.6 (3.3–4.0)
Any rescue therapy	91 (74)	–	–	–	35 (97)	–	4 (29)	–
Nitric oxide, %	72	19	32	15	89	–	7	–
Prone position, %	45	34	20	28	67	–	21	–
Duration of ECMO, days	11 (8–22)	9 (6–12)	10 (7–15)	10 (7–17)	20 (9–38)	9 ± 1	9 (4–11)	16 (9–30)
Mortality, n (%)	44 (36)	22 (28)	17 (25)	14 (29)	6 (17)	6 (40)	9 (64)	2 (15)

BMI: body mass index; SOFA: sequential organ failure assessment; MV: mechanicalventilation.

Data are given as mean ± SD or median (interquartile range).

<sup>5</sup>Winter 2009–2010: 73 patients, winter 2010–2011: 50 patients.

<sup>£</sup>80 patients were transferred to Leicester for consideration to receive ECMO and 69 received the device.



**Table 5 Studies of ECMO for H1N1-associated ARDS reporting on ≤ 10 patients**

	Roncon [42]	D'Ancona [38]	Roch [41]	Hou [45]	Bonastre [47]	Turner [44]	Chan [37]	Freed [39]
Country	Portugal	Italy	France	China	Spain	USA	Hong Kong	Canada
Patients, n	10	10	9	9	9	7	7	6
Study design	Case series	Case series	Case series	Case series	Case series	Case series	Case series	Case series
Number of centers	1	1	1	1	5	1	3	4
Age, years	40 (36–47)	36 (23–55)	49 (26–57)	31 ± 11	36 (28–42)	24 (16–25)	42 (39–50)	33 ± 7
BMI, kg/m <sup>2</sup>	–	26 (21–48)	30 (25–80)	–	–	27 (26–29)	26 (26–27)	33 ± 7
Pregnant or postpartum	1(10)	0 (0)	1 (11)	4 (44)	–	1 (14)	0 (0)	–
SOFA	–	–	9 (8–10)	–	–	–	–	–
Interval MV-ECMO, d	6.5 (2.2–12.2)	–	0.5 (0.25–4.0)	6 (2–10)	5 (2–7)	6.0 (1.5–12.5)	–	5.0 (2.5–8.3)
Pre-ECMO parameter								
pH	7.33 (7.28–7.38)	–	7.17 (7.04–7.25)	–	–	–	7.30 (7.19–7.36)	7.31 ± 0.05
PaO <sub>2</sub> /FiO <sub>2</sub> , mmHg	69 (56–84)	–	52 (50–60)	53 (45–64)	66 (64–102)	57 (51–62)	56 (53–71)	58 ± 17
Plateau pressure, mmHg	35 (32–36)	–	31 (30–35)	–	–	–	33 (30–35)*	44 ± 42*
Lung injury score	3.5 (3.3–3.8)	–	3.6 (3.3–3.7)	3.6 (3.25–3.75)	–	–	3.8 (3.8–3.9)	–
Any rescue therapy, %	70	100	–	–	–	100	14	100
Nitric oxide, %	60	–	67	–	–	100	0	67
Prone position, %	10	–	22	–	–	0	14	33
Duration of ECMO, days	22 (14–32)	–	9 (4–14)	18 (3–90)	6 (5–22)	13 (8–37)	6 (6–10)	15 (14–15)
Mortality, n (%)	4 (40)	5 (50)	5 (56)	4 (44)	5 (56)	2 (28)	1 (14)	2 (33)

BMI: Body mass index; SOFA: Sequential Organ Failure Assessment; MV: mechanical ventilation; Data are given as mean ± SD or median (interquartile range). \*Peak pressure.

**Table 6 Studies reporting on ECCO<sub>2</sub>R for ARDS**

	Gattinoni [67]	Morris [14]	Bein [11]	Flörchinger [69]	Brunet [87]	Muellenbach [88]	Nierhaus [89]	Cho [90]	Conrad [91]	Iglesias [68]
Country	Italy	USA	Germany	Germany	France	Germany	Germany	Korea	USA	Spain
Design	Case series	RCT	RCT	Case series	Case series	Case series	Case series	Case series	Case series	Case series
Prospective	Y	Y	Y	Y	Y	N	N	Y	Y	Y
Setting	Single	Multit	Multi	Single	Single	Single	Single	Single	Multi	Single
Quality assessment <sup>5</sup>	–	RCT5	RCT6	–	–	–	–	–	–	–
Type of CO <sub>2</sub> removal device, AV/W	W	W	AV	AV	W	AV	AV	AV	AV	AV
Patients received ECCO <sub>2</sub> R, n	43	21	40	159	23	22	13	11	8	7
Years	1980–1985	1987–1991	2007–2010	1996–2007	1989–1991	2002–2006	–	2010	1997–1999	2005–2006
Age, years			50 ± 12	44 ± 17	29 ± 10	38 ± 15	52 ± 19	58 ± 15	44 ± 8	53.7 ± 16.0
SOFA score			–	159	15 ± 5	–	–	8.8 ± 1.8	–	–
Pre-CO <sub>2</sub> removal										
PO <sub>2</sub> /FiO <sub>2</sub> , mmHg	67		152 ± 37	72 ± 37	84 ± 30	61 (47–85) <sup>5</sup>	100 ± 29	110 ± 36.6	–	90
PCo <sub>2</sub> , mmHg	49 ± 11		57 ± 12	65 ± 24	56 ± 20	65 (54–72) <sup>5</sup>	80 ± 23	84 ± 23	90.8 ± 7.5	70
Plateau pressure, cmH <sub>2</sub> O	–		29 ± 5	37 ± 6*	51 ± 9*	40 (36–46)** <sup>5</sup>	34 ± 3*	30.1 ± 7.1	–	22.0 ± 7.4
Lung injury score	–		2.8 ± 0.7	–	3.4 ± 0.4	3.5 (3–3.7)	–	–	–	2.9 ± 0.3
Delay MV – extracorporeal CO <sub>2</sub> removal, days	–		<7	7 ± 13	9.2 ± 7.7	1 (0.5–1.9)	9.4 ± 10.2	8.6 ± 12.6	–	4 ± 2
Post-cannulation PCo <sub>2</sub> (24 h), mmHg	–		–	35 ± 7	41 ± 7	39 (36–42) <sup>5</sup>	54 ± 19	40.7 ± 10.2	51.8 ± 3.1	45
Length of CO <sub>2</sub> removal device, days	8 ± 5		7.4 ± 4.0	8 ± 6	13 (1–55)	5.3 (3.2–8.2)	12 ± 22	8.6 ± 9.4	–	4.3 ± 2.5
Serious complication, n (%)	3 (7)		3 (7)	25 (16)	5 (22)	5 (23)	2 (15)	3 (27)	0 (0)	1 (14)
Ischemia lower limb	–		1 (2)	13 (8)	–	3 (14)	0	0	0	0
Compartmental syndrome	–		–	4 (2.5)	–	1 (4)	0	0	0	0
Cannula thrombosis	–		–	8 (5)	–	–	0	0	0	1
Mortality, n (%)	22 (51)	7 (33)	7 (17)	104 (65)	12 (52)	6 (27)	7 (54)	9 (82)	4 (50)	1 (14)

AV: arteriovenous; W: veno-venous; Multi: multicenter; MV: mechanical ventilation; N: no; RCT: randomized controlled trial; SOFA: Sequential Organ Failure Assessment; Y: yes; \*Peak pressure; <sup>5</sup>RCT quality was graded using a nine-point scale combining elements from Jadad's [21] and Chalmers' scales [23,24] whereas the validity of case-controlled studies was appraised with the Newcastle-Ottawa scale [25]. Data are given as mean ± SD or median (interquartile range).

control group were treated conventionally at designated treatment centers [18]. The primary endpoint combining mortality or severe disability 6 months after randomization was lower for the 90 patients randomized to the ECMO group (37% vs. 53%,  $p = 0.03$ ). However, the results of that trial should be analyzed carefully. First, 22 patients randomized to the ECMO arm did not receive ECMO (died before or during transport, improved with conventional management at the referral center or had a contraindication to heparin). Second, no standardized protocol for lung-protective mechanical ventilation existed in the control group and the time spent receiving 'protective' mechanical ventilation was significantly higher in the ECMO arm. Third, more patients received corticosteroids in the ECMO group.

#### **ECMO and ARDS: retrospective series using the latest technology**

In the most recent series, patients benefited from the latest ECMO technology, which includes a centrifugal pump, a polymethylpentene membrane oxygenator and tubing with biocompatible surface treatment. Mortality rates range from 36 to 56% in the studies performed in the last 15 years and reporting outcomes of >30 ECMO patients (Tables 1 and 2). Interestingly, ECMO was provided through a mobile ECMO rescue team in some of these studies. For example, in a series of 124 patients treated at a Danish center between 1997 and 2011 [31], survival was 71% and 85% of these patients received ECMO via a mobile unit before being transferred to the referral hospital. Similarly, in the Regensburg cohort, 59/176 received ECMO at another hospital by a mobile unit [32]. In a multicenter French cohort of 140 patients treated between 2008 and 2012, 68% patients were retrieved via a mobile ECMO team and their prognosis was comparable to those who received VV-ECMO support in their initial hospital [33].

ECMO support may also cause frequent, severe and potentially life-threatening complications (Table 2), such as bleeding, infections, intravascular hemolysis, thrombocytopenia or consumption coagulopathy [26,33-36].

#### **Results of ECMO for pandemic influenza A (H1N1)-associated ARDS**

Mortality rates ranged from 14 to 64% in the 16 studies from 11 countries reporting on the experience of ECMO for influenza A(H1N1)-associated ARDS (Tables 4 and 5) [15-17,33,37-48]. The Australia and New Zealand collaborative group (ANZICS) was the first to report its experience [15]. Despite extreme disease severity at the time of ECMO initiation (median  $\text{PaO}_2/\text{FiO}_2$  ratio 56 mmHg, median positive end-expiratory pressure [PEEP] 18  $\text{cmH}_2\text{O}$  and median lung injury score [LIS] of 3.8), only 25% of the 68 ECMO patients died. A British collaborative

cohort series [16] depicted the outcome of 80 patients transferred into ECMO referral centers in the United Kingdom of whom 69 received ECMO. Mortality in this cohort was 27.5%. A propensity-matched analysis comparing survival of patients referred for consideration of ECMO to other ARDS patients showed better outcomes for referred patients. By contrast, mortality of propensity-matched patients treated conventionally was comparable to that of ECMO patients in French ICUs of the REVA network. However, only 50% of ECMO patients were successfully matched with control ARDS patients, while unmatched ECMO patients were younger, suffered more severe respiratory failure and had considerably lower mortality [17]. Interestingly, a higher plateau pressure under ECMO was independently associated with mortality, indicating for the first time that an ultraprotective ventilation strategy with reduction of plateau pressure to around 25  $\text{cmH}_2\text{O}$  following ECMO installation might improve outcomes. Lastly, mortality was 29% in a cohort of 49 proven influenza A(H1N1) patients from the 14 ECMO centers of the ECMO-NET Italian collaborative group [48]. In this series, patients ventilated for less than 7 days before ECMO initiation had a significantly higher survival.

#### **Mortality risk factors and outcome prediction for ECMO candidates**

Factors associated with poor outcomes after ECMO for acute respiratory failure include older age [26,27,30,32,33,49,50], a greater number of days of mechanical ventilation before ECMO establishment [26,27,30,33,50], a higher number of organ failures [26,27,30,32,33,49,50], low pre-ECMO respiratory system compliance [50], and immunosuppression [33,50,51]. Predictive survival models have been recently developed that might help clinicians select appropriate candidates for ECMO [33,49-52]. For example, the Respiratory Extracorporeal Membrane Oxygenation Survival (RESP) score [50], constructed on data extracted from a large multicenter international population ( $n = 2,355$ ), computes 12 simple pre-ECMO parameters, to provide a relevant and validated tool predicting survival after ECMO for acute respiratory failure. Cumulative predicted hospital survival rates were 92, 76, 57, 33 and 18% for five RESP-score risk classes, I ( $\geq 6$ ), II (3 to 5), III ( $-1$  to 2), IV ( $-5$  to  $-2$ ) and V ( $\leq -6$ ), respectively.

#### **Volume-outcome effect and ECMO activity organization**

Recent analyses of large pediatric databases have suggested a significant relationship between the volume of patients treated by center and ECMO patient prognosis [53-55]. ECMO case-series published after the pandemic influenza A(H1N1) might also allow a comparative analysis of worldwide results obtained for a very homogeneous disease (Tables 4 and 5). These data suggest that the

best results were obtained for patients managed in expert centers treating a sufficient number of patients and in countries where ECMO activity was organized and regulated, as was the case in the United Kingdom [56], Italy [57] and in Australia and New Zealand [58]. A recent position paper [59] by an international group of physicians with expertise in ECMO for severe respiratory failure advocated for regional and inter-regional organization of ECMO activity through networks of hospitals around an ECMO referral center with a mobile ECMO unit [34,60,61] to retrieve the most severe ARDS patients. This group also suggested that at least 20 ECMO cases should be performed per year at each referral center [59]. Furthermore, high volume and expert referral centers may provide better prevention and management of the severe complications that can occur during long ECMO runs (Table 2).

#### Long term outcomes after ECMO

Durations of intensive care and hospital stays of ECMO patients are long and frequently exceed one month [26], [33]. Thus, evaluation of the impact of such complex therapy on long-term pulmonary function, quality of life and psychological status appears crucial in the decision process to use ECMO in ARDS patients. To date, long-term prognosis after ECMO for ARDS has rarely been evaluated. Linden et al. reported long-term outcomes of 21 ARDS survivors rescued with ECMO [62]. In this study, most of the patients had limited fibrosis lesions on CT scan. Respiratory function tests were within normal limits. However, patients reported deterioration in pulmonary symptoms measured by the St George Respiratory Questionnaire, although these symptoms were comparable to those reported in other series of ARDS patients treated conventionally. Similarly, patients in the ECMO arm of the CESAR trial [18] exhibited comparable or better health-related quality of life scores (measured by the SF-36 questionnaire) than those reported by patients with ARDS treated with conventional management [63,64]. Exertional dyspnea was reported by 50% and 40% of 12 influenza A(H1N1) ECMO patients and 25 controls, respectively [65]. Anxiety and depressive symptoms were reported by 50% and 28% of ECMO patients, respectively, whereas 41% were at risk of post-traumatic stress disorder (PTSD) [65]. By contrast, results of the Melbourne group were poorer, with only 26% of long-term survivors having returned to their previous work at eight-month-follow-up [66]. Similar to previous studies, mean SF-36 scores in the ECMO population were lower than these previously described with ARDS survivors in the domains of general health, mental health, vitality and social function. Lastly, the largest study published to date was reported by Schmidt et al. [33] on a population of 84 6-month survivors. In that series, 36%

of the patients reported exertional dyspnea, whereas 30% were still receiving pulmonary treatments after a median 17-month follow-up. Health-related quality of life evaluation in 80% of the 6-month survivors revealed satisfactory mental health but persistent physical and emotional-related difficulties, with anxiety, depression or PTSD symptoms reported by 34, 25 and 16%, respectively.

#### Results of extracorporeal CO<sub>2</sub> removal techniques for ARDS patients

To date, studies on ECCO<sub>2</sub>R in ARDS patients are scarce and mostly small retrospective case series (Table 6). Gattinoni et al. reported in 1986 the first cohort of 43 patients with severe ARDS treated with veno-venous, low flow (200–300 ml/min) ECCO<sub>2</sub>R, which needed a boot volume of almost two liters of blood [67]. In this series, ECCO<sub>2</sub>R duration was 5 days, daily blood losses were large (> 1,800 ml/24 hours) and survival was 49%. A randomized study using the same technology was carried out in the early 1990s by Morris et al. [14]. It was stopped for futility after the enrolment of only 40 patients and mortality was 67% in the 21 patients randomized to ECCO<sub>2</sub>R. In the 2000s, case series, which used the pumpless arteriovenous shunt (extracorporeal interventional lung assist, iLA, Novalung®, Heilbronn, Germany) were published. Iglesias et al. [68] reported the outcome of seven patients with ARDS after pneumonectomy. The ECCO<sub>2</sub>R device was left in place for four days, CO<sub>2</sub> removal was 255 ml/min allowing significant reduction in tidal volume and 6/7 patients survived (Table 6). In a larger German cohort of 156 patients, a higher mortality was reported (65%). Of note, 16% of the patients experienced serious complications in that cohort, particularly leg ischemia related to femoral arterial cannulation and need for higher dose catecholamines (Table 6) [69].

The concept of ultraprotective mechanical ventilation was tested in a proof-of concept trial, with CO<sub>2</sub> removal performed by a modified veno-venous hemofiltration platform. In 10 patients with plateau pressure of 28–30 cmH<sub>2</sub>O at baseline, ECCO<sub>2</sub>R allowed a reduction of tidal volume (from 6 to 4 ml/kg) and of plateau pressure (from 29 to 25 cmH<sub>2</sub>O), while maintaining PaCO<sub>2</sub> around 50 mmHg [19]. This protective ventilation strategy was also associated with a significant reduction in pro-inflammatory cytokine levels in bronchoalveolar (BAL) fluid. This ultraprotective ventilation strategy was recently evaluated in the Xtravent trial [11], which randomized 79 patients to conventional mechanical ventilation using the ARDSNet strategy [70] or to tidal volume reduction to 3 ml/kg permitted by CO<sub>2</sub> removal with the Novalung AV pumpless ECCO<sub>2</sub>R device. The numbers of ventilator-free days at day 60 were not different between groups. However, a post-hoc subgroup analysis revealed that

patients with lower PaO<sub>2</sub>/FiO<sub>2</sub> ( $\leq 150$  mmHg) at randomization had significantly more ventilator-free days at days 28 and 60 and were more rapidly weaned from mechanical ventilation.

### Conclusion and perspectives

We report the results of 56 studies (including 4 RCTs) evaluating extracorporeal gas exchange techniques (ECMO or ECCO<sub>2</sub>-R) to treat moderate to severe acute respiratory failure in adult patients. Major heterogeneity in study populations, disease severity, type of device used and time at which studies were performed creates insuperable hurdles to design relevant meta-analyses. Results of the most recent randomized CESAR trial, which was conducted in the UK from 2001 to 2006, suggested that a strategy of transfer to an ECMO referral center for consideration to receive ECMO was associated with better outcomes. However, that trial was highly criticized for methodological limitations. Additionally, non-randomized case-series of ECMO, including propensity-matched case-control studies, are prone to important selection biases weakening interpretation of their results. Although early implementation of VV-ECMO in severe ARDS patients might allow significant reduction in ventilator-induced lung injury (VILI) and may rescue patients dying of refractory hypoxemia, more evidence is urgently needed to evaluate the actual impact of the technique on patient-centered outcomes compared to optimization of conventional treatments, including prone positioning [2]. This is the main objective of the ongoing international multicenter randomized Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome (EOLIA) trial (ClinicalTrials.gov Identifier: NCT01470703), which will test the efficacy of early VV-ECMO in patients with severe ARDS with tight control of mechanical ventilation in the control group, initiation of ECMO prior to transportation to ECMO centers, and the use of ECMO in every patient randomly assigned to receive it [71].

Pathophysiological, experimental and clinical data suggest that an 'ultraprotective' mechanical ventilation strategy reducing tidal volume to 3–4 ml/kg predicted body weight and plateau pressure to  $< 25$  cmH<sub>2</sub>O may further reduce VILI and ARDS-associated morbidity and mortality in less severe ARDS patients. Hypercapnia induced by tidal volume reduction in this setting might be efficiently controlled by the latest generation low-flow, venovenous ECCO<sub>2</sub>R devices, which are more efficient, more biocompatible and associated with fewer hemorrhagic complications because they require less anticoagulation than devices evaluated in the 1980s and 90s, which did not achieve significant mortality reduction. However, the uncritical and large adoption of this strategy is premature and problematic without rigorous evaluation of associated risks and benefits. This will be the objective of the large

randomized Strategy of Ultra Protective lung ventilation with Extracorporeal CO<sub>2</sub> Removal for New-Onset moderate to severe ARDS (SUPERNOVA) trial, which will test the benefits of early tidal volume and plateau pressure reduction allowed by the latest generation ECCO<sub>2</sub>R device in patients with moderate forms of ARDS [72].

Lastly, future studies of extracorporeal gas exchange should also include detailed evaluation of physical and psychosocial rehabilitation that could lead to improved long-term health-related quality of life in this population of patients.

### Abbreviations

ARDS: Acute respiratory distress syndrome; AV: Arteriovenous; BMI: Body mass index; ECCO<sub>2</sub>R: Extracorporeal carbon dioxide removal; ECMO: Extracorporeal membrane oxygenation; ELSO: Extracorporeal life support organization; ICU: Intensive care unit; LIS: Lung injury score; MV: Mechanical ventilation; PEEP: Positive end-expiratory pressure; PRISMA: Preferred reporting items for systematic reviews and meta-analyses; RCT: Randomized control trial; RESP: Respiratory extracorporeal membrane oxygenation survival; SOFA: Sequential organ failure assessment; VILI: Ventilator-induced lung injury; VV: Venovenous.

### Competing interests

Pr Combes is the primary investigator of the EOLIA trial, NCT01470703, a randomized trial of VV-ECMO supported in part by MAQUET. Pr Combes has received honoraria for lectures by MAQUET, BAXTER AND ALUNG. The other authors declare that they have no competing interests.

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