Spontaneous Breathing during Extracorporeal Membrane Oxygenation in Acute Respiratory Failure

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ABSTRACT

Background: We evaluate the clinical feasibility of spontaneous breathing on extracorporeal membrane oxygenation and the interactions between artificial and native lungs in patients bridged to lung transplant or with acute exacerbation of chronic obstructive pulmonary disease (COPD) or acute respiratory distress syndrome.

Methods: The clinical course of a total of 48 patients was analyzed. Twenty-three of 48 patients were enrolled in the prospective study (nine bridged to lung transplant, six COPD, and eight acute respiratory distress syndrome). The response to the carbon dioxide removal was evaluated in terms of respiratory rate and esophageal pressure swings by increasing ("relief" threshold) and decreasing ("distress" threshold) the extracorporeal membrane oxygenation gas flow, starting from baseline condition.

Results: Considering all 48 patients, spontaneous breathing extracorporeal membrane oxygenation was performed in 100% bridge to lung transplant (9 of 9 extubated), 86% COPD (5 of 6 extubated), but 27% acute respiratory distress syndrome patients (6 of 8 extubated; $P < 0.001$) and was maintained for 92, 69, and 38% of the extracorporeal membrane oxygenation days ($P = 0.021$), respectively. In all the 23 patients enrolled in the study, gas flow increase (from 2.3 ± 2.2 to 9.2 ± 3.2 l/min) determined a decrease of both respiratory rate (from 29 ± 6 to 8 ± 9 breaths/min) and esophageal pressure swings (from 20 ± 9 to 4 ± 4 cm H_2O; $P < 0.001$ for all). All COPD and bridge to lung transplant patients were responders (reached the relief threshold), while 50% of acute respiratory distress syndrome patients were nonresponders.

Conclusions: Carbon dioxide removal through extracorporeal membrane oxygenation relieves work of breathing and permits extubation in many patients, mainly bridge to lung transplant and COPD. Only few patients with acute respiratory distress syndrome were able to perform the spontaneous breathing trial, and in about 50% of these, removal of large amount of patient's carbon dioxide production was not sufficient to prevent potentially harmful spontaneous respiratory effort. **(Anesthesiology 2017; 126:678-87)**

THE promising outcomes during the 2009 influenza A (H1N1) pandemic[1] and the results of the well-known U.K. multicenter randomized trial[2] have renewed interest in extracorporeal membrane oxygenation (ECMO). Technical advances in centrifugal pumps, polymethylpentene membrane oxygenators, and heparin-bonded circuits have improved safety with this technique that might be even considered an alternative to invasive mechanical ventilation (IMV).[3] "Awake ECMO" is the name frequently used to indicate this alternative strategy of ECMO without IMV.[3]

ECMO in conscious, spontaneously breathing patients is increasingly applied in patients awaiting lung transplantation.[4–7] Reports have also been published describing this strategy in patients with acute exacerbation of chronic obstructive pulmonary disease (COPD).[8–13] Finally, respiratory support with ECMO, in combination with spontaneous breathing, has been employed in acute respiratory distress syndrome (ARDS), both clinically and experimentally.[14–16]

What We Already Know about This Topic

- Extracorporeal membrane oxygenation (ECMO) is used in severe acute respiratory distress syndrome or chronic obstructive pulmonary disease exacerbation or as a bridge to lung transplantation. Data on tolerance to spontaneous ventilation (or extubation) during ECMO are sparse.

What This Article Tells Us That Is New

- Spontaneous breathing was possible in most during bridge to transplant (100%) or chronic obstructive pulmonary disease (86%) but in less than 30% of acute respiratory distress syndrome, and in half of these, dyspnea persisted despite carbon dioxide removal.

Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org).

Submitted for publication July 29, 2016. Accepted for publication January 6, 2017. From the Dipartimento di Anestesia, Rianimazione ed Emergenza Urgenza, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milan, Italy (S.C., N.B., E.S., D.T., A.L., A.P.); and Dipartimento di Fisiopatologia Medico-Chirurgica e dei Trapianti, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, and Università degli Studi di Milano, Milan, Italy (G.M.R.); and Department of Anesthesia and Intensive Care, Georg-August-Universität, Göttingen, Germany (L.G.). The work was performed at the Intensive Care Unit "E.Vecla," Fondazione IRCCS Cà Granda, Ospedale Maggiore Policlinico, Milan, Italy.

 Anesthesiology 2017; 126:678-87

<zdoi;10.1097/ALN.0000000000001546>

The rationale for this approach could be already found in some experimental models published in the late 1970s by Kolobow *et al.*,[17] demonstrating that pulmonary ventilation could be affected by changing extracorporeal removal of carbon dioxide, up to apnea when the total metabolic carbon dioxide production (VCO_2) was cleared by ECMO.

However, the rationale for "awake ECMO" treatment is different for each type of acute respiratory failure (ARF).[3] In patients bridged to lung transplant on ECMO, the avoidance of intubation and IMV and the maintenance of physical activity seem to improve survival and to be associated with a less complicated clinical course after transplantation.[6,7] In patients with acute exacerbation of COPD, the rationale is mainly to reduce the need for ventilation through the native lung, aiming for natural lung deflation, while intubation and IMV potentially initiate a vicious circle that leads to the worsening of dynamic hyperinflation, the need for sedation and sometimes paralysis, and lastly, impossible weaning. In ARDS patients, the possibility to reach or maintain spontaneous breathing on ECMO could prevent the complications associated with intubation and IMV, such as barotrauma and volutrauma, the circulatory impact of sedation and mechanical ventilation, the diaphragmatic dysfunction, the risk of ventilator-acquired pneumonia, and sepsis.[18–20]

Is it then possible to manage all the patients bridged to lung transplant or with acute exacerbation of COPD or ARDS on ECMO with the spontaneous breathing approach? Do these groups of ARF, with their different pathophysiology and respiratory mechanics, behave the same way when supported with ECMO on spontaneous breathing?

The aim of the current study in these three major categories of ARF was to evaluate (1) the clinical feasibility of spontaneous breathing on ECMO and (2) the interactions between the artificial and the native lung.

Materials and Methods

In January 2010, we started to use ECMO in conscious, spontaneously breathing patients as an alternative to IMV. We considered the period from January 2010 to May 2012 as a learning period of this new approach. As soon as we acquired skill in the management of awake patients on ECMO, we began the study protocol as follows. From June 2012 to December 2014, we tested the feasibility of spontaneous breathing during ECMO support in all patients of the three groups (bridge to lung transplant, COPD, and ARDS). Patients who were treated with this approach were enrolled in the study. The study protocol and data analysis were approved by our local institutional review board. Informed consent was obtained from subjects enrolled in the study as soon as they recovered from acute critical illness.

During their clinical course, the nonintubated patients on ECMO support often alternated noninvasive ventilation (NIV), continuous positive airway pressure (CPAP), or oxygen supplementation through a facemask. If the patients were already sedated, intubated, and on IMV when ECMO started, they were awakened and weaned from the IMV as soon as the clinical conditions allowed, with particular attention to airway protection, ability to cough, and control of fever. Intensive respiratory physiotherapy combined with fiber-optic bronchoscopy was performed in order to maximize adequate pulmonary toilet mainly in patients with cystic fibrosis. Short-acting sedatives (propofol and remifentanil) were used to facilitate the awakening process. Attempts for weaning from sedation and IMV were made during the first 5 to 7 days on ECMO, unless pulmonary plasma leakage, severe hemodynamic impairment, or major bleeding were present (exclusion criteria).

The extracorporeal respiratory support was performed with a venovenous bypass. Peripheral cannulation of the two common femoral veins was performed percutaneously. In awake patients, the procedure was performed under mild sedation and local anesthesia. Technical details of ECMO configuration are described in the Online supplementary material (Supplemental Digital Content 1, http://links.lww.com/ALN/B382).

Data Collection

All patients had a nasogastric tube in place with an integrated esophageal balloon as in our common clinical practice. We recorded the respiratory rate (RR, breaths/min) and changes in pleural pressure as measured by tidal esophageal pressure (P_{es}) swings (an index of work of breathing).[21]

We recorded the main hemodynamic parameters, cardiac output (CO; by thermodilution from the Swan–Ganz catheter), and arteriovenous oxygen difference ($avDO_2$). We then computed (1) the extracorporeal carbon dioxide removal (ECMO-VCO_2), multiplying the carbon dioxide percentage in the sweep gas from the ECMO circuit by the sweep gas flow (GF) itself; (2) the total oxygen uptake ($\dot{V}O_2$), as the patient $\dot{V}O_2$ (patient $avDO_2$ × CO) plus the ECMO $\dot{V}O_2$ (ECMO $avDO_2$ × BF, *i.e.*, blood flow [BF]); (3) the ECMO-VCO_2 as a percentage of the total VCO_2, which was considered equal to the total $\dot{V}O_2$, assuming a respiratory quotient of 1, as previously reported[8]; and (4) the pulmonary shunt fraction (%).[22]

Patients in the ARDS group underwent a chest computed tomographic scan while on IMV with computation of the potentially recruitable lung (defined as the difference between nonaerated lung tissue weight at end-expiration and end-inspiratory 45 cm H_2O airway pressure, expressed as a percentage of the total lung tissue weight), the total lung weight, and the amount of nonaerated tissue (as an index of the severity of ARDS).[23]

The baseline characteristics of the patients before the ECMO implantation and the setting of the ECMO support and the sequential organ failure assessment score excluding the respiratory subscore at the first day on ECMO were recorded.

Study Design

To be enrolled in the study, patients had to be cooperative with a Richmond Agitation-Sedation Scale (RASS) score between −1 and +1. Anxiolytics (alprazolam) and antipsychotics (haloperidol) were used to reach this target, if needed.

In order to evaluate the spontaneous breathing response to the carbon dioxide removal, we changed the ECMO GF. Starting from baseline condition as set by the physicians (basal GF), we decreased GF to reach a RR equal to or greater than 30 breaths/min and/or P_{es} swing equal to or greater than 20 cm H_2O (low GF, "distress"). Then we increased GF to obtain a spontaneous RR equal to or lower than 10 breaths/min with a P_{es} swing equal to or smaller than 8 cm H_2O (high GF, "relief"). A patient who did not reach the threshold values of "relief" at the highest GF (as high as 12 to 15 l/min) was considered a "nonresponder." Data were recorded after 30 min of stabilization.

During the study test, NIV was not allowed because it provides a ventilatory support, while oxygen supplementation or CPAP settings were maintained unchanged (Supplemental Digital Content 2, Table 1S, http://links.lww.com/ALN/B383), as well as the ECMO BF. The study test was performed within 48 h from the beginning of the spontaneous breathing on ECMO.

Statistical Analysis

Based on previous (unpublished) experience, we anticipated that maintaining spontaneous breathing in patients with ARDS would have been particularly difficult. We then planned to enroll 30 of these patients, considering such a population large enough to provide valid preliminary data in a reasonable period of time (less than 3 yr). In the meanwhile, we also considered enrolling all other consecutive patients treated with ECMO for respiratory failure at our institution, according to inclusion and exclusion criteria.

Data are reported as mean and SD (continuous variables), median and interquartile range (ordinal variables), or proportion. They were compared between groups with two-tailed Student's *t* test, Mann–Whitney U test, (repeated-measure) one-way ANOVA, (repeated-measure) one-way ANOVA on ranks, or Freeman–Halton extension of the Fisher exact test. Strength of association between (normally distributed) variables was measured with linear regression analysis and expressed as R^2. $P < 0.05$ indicates statistical significance (SigmaPlot 11.0; Jandel Scientific Software, USA).

Results

Feasibility of Spontaneous Breathing

During the study period, considering the whole population of patients supported with ECMO for ARF, we performed the spontaneous breathing ECMO in 100% bridge to lung transplant, 86% COPD, but 27% ARDS patients ($P < 0.001$; fig. 1), which means a total of 52% patients were treated with this strategy. Only one COPD patient failed the awake strategy because of major neurologic impairment (Glasgow Coma Scale 10). In 13 ARDS patients (43%), the spontaneous breathing ECMO strategy was not even tested due to the presence of one or more exclusion criteria (nine patients had pulmonary plasma leakage, four had severe hemodynamic impairment, and two had major bleeding). In nine ARDS patients (30%), the spontaneous breathing ECMO was tried but failed due to one or more of the following reasons: six patients continued to have severe respiratory distress and concomitant agitation (RASS 3 to 4), four developed hemodynamic instability, four showed neurologic problems (seizures or uneffective sedatives washout, RASS less than or equal to −3), one was unable to handle pulmonary secretion with cough, and one subsequently developed major bleeding.

Baseline characteristics of the patients in the three groups are listed in table 1 (Supplemental Digital Content 3, Table 2S, http://links.lww.com/ALN/B384). Table 2 shows the baseline characteristics of the ARDS patients on spontaneous breathing compared to ARDS patients on IMV.

The mean duration of ECMO support was 8 ± 4, 10 ± 6, and 11 ± 9 days, respectively, for bridge to lung transplant, COPD, and ARDS patients.

The awake patients of the bridge to lung transplant, COPD, and ARDS groups were maintained on spontaneous breathing for 92, 69, and 38% of the ECMO days, respectively ($P = 0.021$). All the bridge to lung transplant patients were intubated and mechanically ventilated in the operating theater before lung transplantation, but one who was

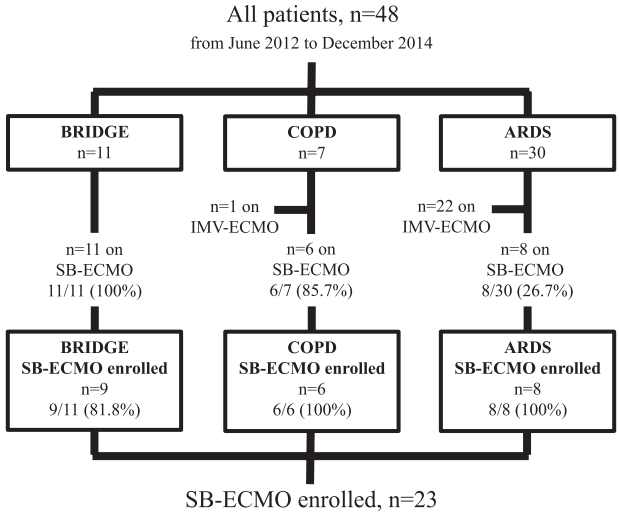

Fig. 1. Algorithm of the overall population, showing the feasibility of the spontaneous breathing on extracorporeal membrane oxygenation (SB-ECMO) and the number of SB-ECMO patients enrolled in the study for each group. ARDS = acute respiratory distress syndrome; BRIDGE = bridge to lung transplant; COPD = chronic obstructive pulmonary disease; IMV = invasive mechanical ventilation.

Table 1. Main Characteristics of the Study Population Before Extracorporeal Membrane Oxygenation Start

	BRIDGE	COPD	ARDS
	n = 11	n = 7	n = 30
Age, yr	38 ± 8	72 ± 6	54 ± 16
Body mass index, kg/m^2	20 ± 4	26 ± 4	26 ± 5
Referred from another hospital, n (%)	2 of 11 (18)	1 of 7 (14)	18 of 30 (60)
Arterial pH	7.23 ± 0.14	7.20 ± 0.08	7.25 ± 0.12
Arterial P_{CO_2}, mmHg	92 ± 27	79 ± 28	62 ± 16
Arterial P_{O_2}/F_{IO_2}, mmHg	152 ± 56	262 ± 138	79 ± 51
Positive end-expiratory pressure, cm H_2O	7 ± 3	8 ± 5	16 ± 4
Mechanical ventilation, n (%)	1 of 11 (9)	5 of 7 (71)	28 of 30 (93)
Length of mechanical ventilation, days	0.1 ± 0.3	1.6 ± 2.4	2.6 ± 3.4
Vasoactive drugs, n (%)	1 of 11 (9)	5 of 6 (83)	16 of 28 (57)
Arterial lactate, mM/l	1.5 ± 1.5	2.7 ± 2.9	3.1 ± 2.6
White blood cells, 10^3/mm^3	20.21 ± 12.49	16.28 ± 5.72	12.37 ± 7.62
C-reactive protein, mg/dl	9 ± 6	7 ± 4	21 ± 11
SOFA score (without respiratory subscore)	0 [0–0]	3 [2–5]	4 [2–6]

Data are reported as mean ± SD, median [interquartile range], or proportions. Missing values: arterial partial pressure of oxygen (P_{O_2})/fraction of inspiratory oxygen (F_{IO_2}; n = 1), positive end-expiratory pressure (n = 1), length of mechanical ventilation (n = 1), vasoactive drugs (n = 3), C-reactive protein (n = 1), and sequential organ failure assessment (SOFA) score (without respiratory subscore; n = 9).

ARDS = acute respiratory distress syndrome; BRIDGE = bridge to lung transplant; COPD = chronic obstructive pulmonary disease; P_{CO_2} = partial pressure of carbon dioxide.

Table 2. Main Characteristics of Patients with ARDS, Who Could or Could Not Be Maintained Spontaneously Breathing, for at Least Some Time, during ECMO

	ARDS: SB Feasible	ARDS: SB Not Feasible	
	n = 8	n = 22	*P* Value
Age, yr	49 ± 18	55 ± 14	0.401
Body mass index, kg/m^2	24.6 ± 4.5	26.5 ± 5.7	0.381
Referred from another hospital, n (%)	3 of 8 (37)	15 of 22 (68)	0.210
Arterial pH before ECMO	7.290 ± 0.091	7.232 ± 0.122	0.239
Arterial P_{CO_2} before ECMO, mmHg	61 ± 19	62 ± 14	0.886
Arterial P_{O_2}/F_{IO_2} before ECMO, mmHg	86 ± 22	76 ± 59	0.048*
Positive end-expiratory pressure before ECMO, cm H_2O	14 ± 2	16 ± 4	0.148
Mechanical ventilation before ECMO, n (%)	6 of 8 (75)	22 of 22 (100)	0.067
Length of mechanical ventilation before ECMO, days	1.1 ± 1.2	3.1 ± 3.8	0.047*
Blood flow on day 1 of ECMO, l/min	2.8 ± 0.4	3.1 ± 0.7	0.302
Gas flow on day 1 of ECMO, l/min	4.4 ± 1.4	5.9 ± 2.5	0.142*
SOFA score (without respiratory subscore) day 1 ECMO	0.5 [0–2]	5.5 [3–9]	< 0.001*
Pulmonary shunt on day 1 of ECMO, %	51 ± 12	54 ± 18	0.737
Lung recruitability, %	30 ± 18	26 ± 13	0.503
Total lung weight, g	1,694 ± 435	2,468 ± 942	0.041*
Nonaerated lung tissue, %	43 ± 25	56 ± 17	0.123
Duration of ECMO, days	12 ± 8	11 ± 10	0.778*
ICU survival, n (%)	6 of 8 (75)	14 of 22 (64)	0.682

Data are reported as mean ± SD, median [interquartile range], or proportions. Groups were compared with Student's *t* test, Mann–Whitney rank sum test, or Fisher exact test. Lung recruitability (not available for three patients), total lung weight (at low airway pressure), and nonaerated lung tissue (at low airway pressure) were obtained from quantitative analysis of lung computed tomography scans. Low airway pressure was 5 cm H_2O in 22 subjects (in both groups) and greater than or equal to 10 cm H_2O in eight subjects (in spontaneous breathing not feasible group).

*Mann–Whitney rank sum test.

ARDS = acute respiratory distress syndrome; ECMO = extracorporeal membrane oxygenation; F_{IO_2} = fraction of inspiratory oxygen; ICU= intensive care unit; P_{CO_2} = partial pressure of carbon dioxide; P_{O_2} = partial pressure of oxygen; SB = spontaneous breathing; SOFA = sequential organ failure assessment.

intubated during the ECMO course because of worsening respiratory failure was deemed ineligible for lung transplant and died. Sixty-seven percent of COPD (three for difficult secretion clearance and one for bleeding) and 50% of ARDS patients (two for persistent respiratory distress, one for new onset of septic shock, and one for difficult secretion clearance) were intubated during the ECMO support. Intensive care unit survival of the awake patients (n = 25) was 91% in bridge to lung transplant, 50% in COPD, and 75% in ARDS patients.

ARDS Subgroup

Considering the ARDS patients (table 2), spontaneous breathing group had a higher arterial partial pressure of oxygen/fraction of inspiratory oxygen ratio and a lower sequential organ failure assessment score. The potentially recruitable lung and the percentage of nonaerated tissue did not differ between the two groups, but the total lung weight was higher in the IMV-ECMO group (table 2). A more detailed description of the spontaneous breathing ARDS patients is provided in the online supplement.

Respiratory Response Induced by Changes in the Sweep Gas Flow

We investigated the effect of changing the sweep GF on spontaneous breathing pattern in 23 patients. Two patients were excluded as they prematurely underwent lung transplantation (fig. 1).

Increasing the sweep GF (and the extracorporeal carbon dioxide removal) led to a constant, but variable, decrease in RR (fig. 2) and P_{es} swings (fig. 3). In the mean time, arterial carbon dioxide tension diminished and arterial pH accordingly rose, pulmonary shunt and arterial oxygenation worsened, while systemic hemodynamics remained quite constant (table 3).

All COPD and bridge to lung transplant patients reached the relief threshold, while 50% of ARDS patients were nonresponders, maintaining unexpectedly high RR (25 ± 1 breaths/min) and P_{es} swings (9 ± 7 cm H_2O) even with the maximum sweep GF, corresponding to a removal of 84 ± 16% of estimated whole-body carbon dioxide production. ARDS responders and nonresponders did not differ in hemodynamics and gas exchange (Supplemental Digital Content 4, Table 3S, http://links.lww.com/ALN/B385).

Table 3 shows the patient respiratory and ECMO parameters at the three sweep GF levels. The ECMO-VCO_2 that allowed to reach the threshold values of "relief" was 59% in COPD, while it was greater than 90% in bridge to lung transplant and ARDS patients. Moreover, in the ARDS group, the GF at the high level was higher than in the other two groups. The ECMO carbon dioxide removal per liter of GF was different in the ARDS compared to the other groups (25.8 ± 5.2 ml · min^{-1} · l^{-1} in bridge to lung transplant, 26.8 ±

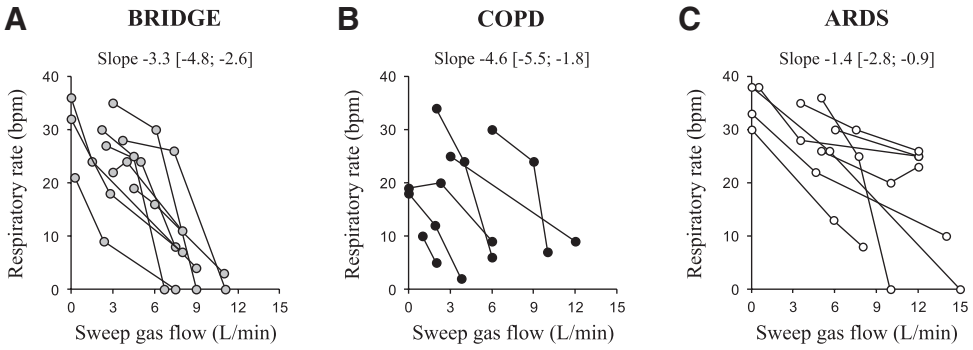

Fig. 2. Spontaneous respiratory rates at different sweep gas flows in patients treated with extracorporeal membrane oxygenation as (*A*) bridge to lung transplant (BRIDGE; n = 9) or because of acute exacerbation of (*B*) chronic obstructive pulmonary disease (COPD; n = 6) or (*C*) acute respiratory distress syndrome (ARDS; n = 8). Individual data are connected with a *line*. The slopes reported on *top* are the median [interquartile range] of individual slopes (the coefficient of the equation obtained with linear regression analysis of individual data). Comparing the median slopes between the three diagnostic categories with one-way ANOVA on ranks yields a $P = 0.066$.

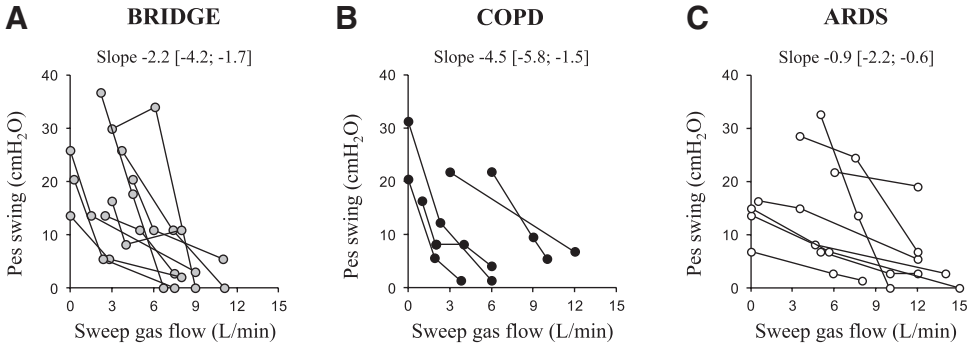

Fig. 3. Spontaneous esophageal pressure (P_{es}) swings at different sweep gas flows in patients treated with extracorporeal membrane oxygenation as (*A*) bridge to lung transplant (BRIDGE; n = 9) or because of acute exacerbation of (*B*) chronic obstructive pulmonary disease (COPD; n = 6) or (*C*) acute respiratory distress syndrome (ARDS; n = 8). Individual data are connected with a *line*. The slopes reported on *top* are the median [interquartile range] of individual slopes (the coefficient of the equation obtained with linear regression analysis of individual data). Comparing the median slopes between the three diagnostic categories with one-way ANOVA on ranks yields a *P* value of 0.074.

Table 3. Response to Changes in Sweep Gas Flow in All Patients Enrolled in the Study and in Each Subgroup

	Low Sweep Gas Flow	Basal Sweep Gas Flow	High Sweep Gas Flow	*P* Value
Sweep gas flow, l/min				
All patients	2.3 ± 2.2	5.1 ± 2.8	9.2 ± 3.2	< 0.001
BRIDGE	2.1 ± 1.7	4.4 ± 1.9	8.6 ± 1.5	
COPD	2.0 ± 2.8	3.5 ± 2.9	6.6 ± 3.8	
ARDS	2.5 ± 2.6	7.1 ± 2.8	11.9 ± 2.2	
Extracorporeal carbon dioxide removal, ml/min				
All patients	91 ± 80	158 ± 59	206 ± 55	< 0.001
BRIDGE	109 ± 78	170 ± 50	218 ± 23	
COPD	69 ± 90	114 ± 59	164 ± 72	
ARDS	83 ± 85	179 ± 59	226 ± 56	
Extracorporeal carbon dioxide removal, %				
All patients	31 ± 28	63 ± 24	85 ± 22	< 0.001
BRIDGE	38 ± 28	72 ± 24	96 ± 7	
COPD	11 ± 19	37 ± 11	59 ± 25	
ARDS	30 ± 31	70 ± 18	92 ± 14	
Respiratory rate, breaths/min				
All patients	29 ± 6	22 ± 6	8 ± 9	< 0.001
BRIDGE	28 ± 6	22 ± 6	4 ± 4	
COPD	25 ± 8	19 ± 7	6 ± 3	
ARDS	33 ± 4	24 ± 5	15 ± 11	
Esophageal pressure swing, cm H_2O				
All patients	20 ± 9	12 ± 7	4 ± 4	< 0.001
BRIDGE	23 ± 8	13 ± 9	3 ± 4	
COPD	20 ± 9	12 ± 6	5 ± 3	
ARDS	18 ± 9	12 ± 9	5 ± 6	
Arterial pH				
All patients	7.41 ± 0.06	7.45 ± 0.04	7.48 ± 0.05	< 0.001
BRIDGE	7.38 ± 0.07	7.42 ± 0.04	7.47 ± 0.06	
COPD	7.40 ± 0.04	7.46 ± 0.03	7.49 ± 0.04	
ARDS	7.46 ± 0.04	7.47 ± 0.04	7.49 ± 0.03	
Arterial carbon dioxide tension, mmHg				
All patients	48 ± 13	44 ± 10	39 ± 8	< 0.001*
BRIDGE	59 ± 9	54 ± 6	47 ± 5	
COPD	44 ± 9	40 ± 6	36 ± 7	
ARDS	37 ± 6	35 ± 7	34 ± 6	
Arterial oxygen tension, mmHg				
All patients	111 ± 58	104 ± 46	81 ± 39	< 0.001*
BRIDGE	129 ± 78	116 ± 59	75 ± 46	
COPD	113 ± 29	106 ± 46	92 ± 38	
ARDS	91 ± 40	89 ± 27	80 ± 34	
Pulmonary shunt, %				
All patients	38 ± 19	41 ± 18	53 ± 22	< 0.001*
BRIDGE	39 ± 21	44 ± 18	63 ± 21	
COPD	30 ± 16	29 ± 19	39 ± 25	
ARDS	42 ± 20	46 ± 16	52 ± 16	
CO, l/min				
All patients	7.3 ± 1.4	7.0 ± 1.4	6.9 ± 1.5	0.122
BRIDGE	7.3 ± 0.7	6.6 ± 0.6	6.4 ± 0.7	
COPD	7.1 ± 0.8	7.1 ± 1.5	7.1 ± 1.1	
ARDS	7.4 ± 2.1	7.2 ± 2.0	7.4 ± 2.2	

Starting from "basal" values (those set by the attending physician), sweep gas flow was either increased ("high") or decreased ("low"), while extracorporeal blood flow was kept constant (2.8 ± 0.5 l/min in all groups). Variables of interest were recorded after 30 min. Data are reported as mean ± SD. *P* values refer to comparison, with one-way repeated measures (RM) ANOVA or one-way RM ANOVA on ranks, between different sweep gas flows in all subjects, considered as a whole. Data recorded from the three subgroups (different pathologies) are shown for descriptive purpose. n = 9 (BRIDGE); n = 6 (COPD), two missing values at low sweep gas flow; n = 8 (ARDS).

*One-way RM ANOVA on ranks.

ARDS = acute respiratory distress syndrome; BRIDGE = bridge to lung transplant; CO = cardiac output; COPD = chronic obstructive pulmonary disease.

5.4 ml · min^{-1} · l^{-1} in COPD, and 19.6 ± 3.7 ml · min^{-1} · l^{-1} in ARDS patients; *P* = 0.025). As shown in figure 4, this finding was reasonably explained by the different carbon dioxide tensions in blood entering the lung membrane,

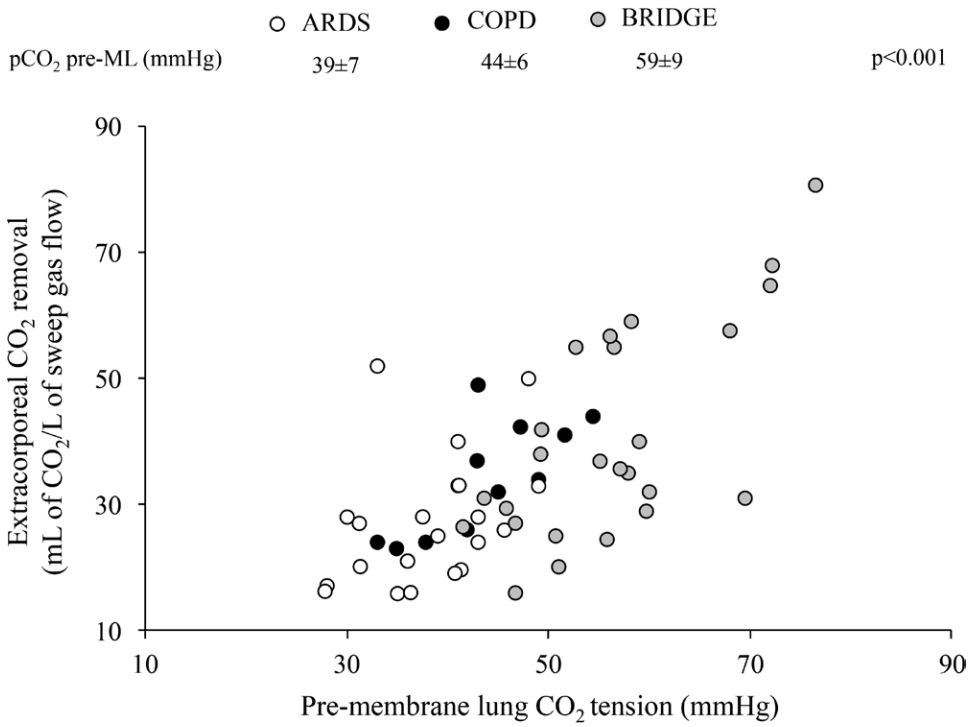

Fig. 4. Extracorporeal carbon dioxide removal per liter of sweep gas flow as a function of carbon dioxide tension in blood entering the membrane lung. Individual data (up to three recordings per patient, excluding those obtained when the sweep gas flow was 0 l/min) were considered as independent and are shown as *dots*. According to linear regression analysis, y = –6.902 + 0.875 × (n = 58; R^2 = 0.479, *P* < 0.001). Carbon dioxide tension in blood entering the membrane lung (P_{CO_2} pre-ML) is also expressed as mean ± SD for each diagnostic category, on *top* of the figure (the *P* value refers to one-way ANOVA). ARDS = acute respiratory distress syndrome; BRIDGE = bridge to lung transplant; COPD = chronic obstructive pulmonary disease.

which was lowest in patients with ARDS. There was no difference in the total V_{O_2} of the three groups.

Discussion

Our investigation compares the spontaneous breathing strategy during ECMO in three different etiologies of ARF: bridge to lung transplant, COPD, and ARDS. Our analysis suggests that the use of ECMO in spontaneously breathing patients as an alternative to intubation and IMV is feasible in bridged to lung transplant and COPD patients, as previously reported by other groups.[4–13] However, the application of this strategy is more complicated in the ARDS patients. This approach appears to be more feasible in ARDS patients with a less severe respiratory failure and with less organ dysfunctions. Nevertheless, by describing the physiologic response of these different types of ARF to the extracorporeal carbon dioxide clearance variations, our study may help explain the different behaviors of the three groups.

The use of ECMO in awake patients was first developed successfully in patients bridged to lung transplant. Some case series have been published recently.[4–7] A study from the Hannover group showed a better survival in the patients treated with ECMO without intubation and IMV compared to the patients invasively ventilated on ECMO.[5] Their own study coined the term "awake ECMO." Currently, in the ECMO centers with a lung transplant program, many of the end-stage respiratory failures, failing NIV therapy, are supported with the awake ECMO approach while waiting for organ allocation. In 2010, we started to apply the awake ECMO strategy to patients bridged to lung transplant, and we quickly realized the huge advantage of this approach in terms of pretransplant conditioning. We recently published our data about the benefit of this strategy in terms of reduced postoperative time on IMV, intensive care unit, and hospital length of stay.[7] Since June 2012, all patients requiring ECMO as bridge to lung transplant at our center have received awake ECMO. Furthermore, they all have been enrolled in the study and responded to the GF increase reducing RR and P_{es} swing. In these patients, you need to remove more than 90% of the total metabolic carbon dioxide production to get complete relief from dyspnea. However, arterial oxygenation decreases and shunt fraction increases at the highest level of extracorporeal carbon dioxide removal, likely because of hypoventilation and derecruitment. We also clinically observed that there is a clear reduction in the ability to cough at the highest GF. Knowing these data, we set an intermediate GF and accept higher RR and P_{es} swing in these patients.

In COPD patients, the extracorporeal carbon dioxide clearance easily allows to reduce respiratory distress. However, the feasibility of this approach seems limited for prolonged

time, as suggested by the high intubation rate we observed. In all COPD patients, we tried to get complete relief from dyspnea sometimes up to apnea with the intention to obtain a lung deflation and thus interrupting the vicious circle of dynamic hyperinflation, as previously shown in a case report published by our group.[8] All patients enrolled in the study responded to the GF rise with a decrease in RR and P_{es} swing. Unlike patients bridged to lung transplant, in COPD patients at the highest GF level, arterial oxygenation shows a downward trend, and shunt fraction seems to increase though not significantly. Indeed, it was possible to correct this side effect with a supplement of inspired oxygen. In our study population, the amount of carbon dioxide that needs to be removed to obtain relief of the dyspnea is much lower in COPD patients compared to the other two groups (60% *vs.* more than 90%). This could be partially explained by the different pathophysiology of COPD. Since the clinical picture is characterized by a lower degree of inflammation and rather a severe dynamic hyperinflation,[24] the extracorporeal clearance of a relatively small amount of carbon dioxide allows to reduce patient ventilation and then solve dynamic hyperinflation. By showing a scarce worsening of oxygenation at the highest GF and the need for a smaller amount of carbon dioxide removal in COPD patients, our data may support the possible use of less-invasive extracorporeal devices that work at low BF rates, while ensuring a carbon dioxide removal ranging from 30 to 60% of the patient's metabolic carbon dioxide production. Some studies have been recently published on the successful application of these simplified systems,[9–13] which also opens a new future perspective in the outpatient use.

There are only few reports in the literature on the use of the awake ECMO in patients with ARDS.[14,15] From our data, the spontaneous breathing ECMO strategy seems to be more difficult to apply in the ARDS patients. In 2.5 years, only 27% of the ARDS patients were successfully managed with the spontaneous breathing ECMO strategy, compared to 86% of the COPD and 100% of the patients bridged to lung transplant. We retrospectively observed that ARDS patients who tolerated spontaneous breathing had better oxygenation, fewer organ dysfunctions, and a lower degree of lung injury as suggested by the computed tomographic data. Nevertheless, only 50% of the patients who could be managed with the spontaneous breathing ECMO strategy and enrolled in the study responded as expected to the acute increase in the sweep GF. Moreover, we found it very difficult to manage these spontaneously breathing patients with early ARDS on ECMO. High levels of positive end-expiratory pressure through CPAP were required in all the ARDS patients in order to limit lung derecruitment and collapse, while the patients in the other two groups demonstrated a limited need for CPAP (Supplemental Digital Content 5, Table 4S, http://links.lww.com/ALN/B386). A possible explanation for the different behavior of the ARDS patients as compared to the other groups may lie in the different pulmonary pathophysiology and in the severity of the respiratory and other organ dysfunctions. In cases of more severe ARDS, the huge degree of inflammation, the parenchymal edema, and the consequent alveolar collapse could not be managed with the patient breathing spontaneously, at least in the earlier stage of the disease. Other organ dysfunctions and septic shock often complicate the clinical picture. In fact, during the early course of severe ARDS, a strategy of deep sedation and paralysis has been shown to improve outcome,[25] likely because it allows a better lung protection.

We also observed that the tension of carbon dioxide in blood entering the oxygenator in the ARDS patients is a limiting factor in optimizing the ECMO performance. The lower the carbon dioxide tension, the higher the GF required to remove a given amount of carbon dioxide. Sometimes the highest level of gas, within security specifications, is not enough. To ameliorate the carbon dioxide removal, some authors are investigating the hypothesis that acidifying the blood entering the oxygenator could enhance the carbon dioxide transfer.[26] The same increase in performance may be obtained by electrodialysis.[27]

It is well known that the application of high volumes and/or high pressures during mechanical ventilation is detrimental.[18,28–30] However, injurious effects have been observed also during spontaneous breathing when ventilation is excessive.[31–35] Then, spontaneous breathing does not necessarily mean prevention of lung injury. We monitored RR and P_{es} swing as indexes of respiratory distress and effort, respectively. High negative values of pleural pressure may develop during inspiration as a consequence of either high-volume spontaneous ventilation or excessive elastic or resistive workload, potentially resulting in "*ventilation*"-induced lung injury.[36] We arbitrarily defined the relief and "distress" threshold,[37] but it is rather difficult to explore what happens between these two extremes. Respiratory monitoring is limited during spontaneous breathing: an important limitation of our study is the lack of respiratory mechanics data, such as tidal volume, airway pressure, and lung and chest wall elastances. More data are needed to define which thresholds for the RR and/or the negative pressure should be considered harmful for the lung. Therefore, the conventional approach with sedation, paralysis, and controlled mechanical ventilation is to be recommended when clinical evaluation suggests that unassisted spontaneous ventilation could induce lung injury, particularly in the early phase of ARDS.[25]

In conclusion, this preliminary and mainly descriptive study suggests that spontaneous breathing can be successfully maintained in most of the patients treated with ECMO as a bridge to lung transplantation or because of an acute exacerbation of COPD. More investigations and experiences are desirable to support the use of the awake ECMO approach in ARDS patients to identify the mechanisms underlying the failure of this strategy and to better select the ARDS patients in whom the spontaneous breathing ECMO strategy could be feasible, useful, and safe.

Acknowledgments

The authors would like to thank the nurses and doctors of the intensive care unit at Ospedale Maggiore Policlinico,

Milan, Italy, who fully managed the patients on ECMO. The authors also underscore the essential role of the physiotherapists in the respiratory and physical care of the conscious, awake, and spontaneous breathing patients on ECMO.

Competing Interests

The authors declare no competing interests.

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