ECMO criteria for influenza A (H1N1)-associated ARDS: role of transpulmonary pressure.

ECMO CRITERIA FOR *INFLUENZA* A (H1N1) - ASSOCIATED ARDS: ROLE OF TRANSPULMONARY PRESSURE[1]

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ABSTRACT (words count: 224)

Purpose: To assess whether partitioning the elastance of the respiratory system (E_{RS}) between lung (E_L) and chest wall (E_{CW}) elastance in order to target values of end-inspiratory trans-pulmonary pressure (P_{PLAT_L}) close to its upper physiological limit (25 cmH_2O) may optimize oxygenation allowing conventional treatment in patients with influenza A (H1N1)-associated ARDS referred for extracorporeal membrane oxygenation (ECMO).

Methods: Prospective data collection of patients with influenza A (H1N1)-associated ARDS referred for ECMO (October 2009-January 2010). Esophageal pressure was used to (a) partition respiratory mechanics between lung and chest wall; (b) titrate positive end expiratory pressure (PEEP) to target the upper physiological limit of P_{PLAT_L} (25 cmH_2O).

Results: Fourteen patients were referred for ECMO. In 7 patients P_{PLAT_L} was 27.2±1.2 cmH_2O; all these patients underwent ECMO. In the other 7 patients, P_{PLAT_L} was 16.6±2.9 cmH_2O. Raising PEEP (from 17.9±1.2 to 22.3±1.4 cmH_2O, P=0.0001) to approach the upper physiological limit of trans-pulmonary pressure (P_{PLAT_L}=25.3±1.7 cmH_2O) improved oxygenation index (from 37.4±3.7 to 16.5±1.4, P=0.0001) allowing patients to be treated with conventional ventilation.

Conclusions: Abnormalities of chest wall mechanics may be present in some patients with influenza A (H1N1)-associated ARDS. These abnormalities may not be inferred from measurements of end-inspiratory plateau pressure of the respiratory system

($P_{PLAT_{RS}}$). In these patients, titrating PEEP on $P_{PLAT_{RS}}$ may overestimate the incidence of hypoxemia refractory to conventional ventilation leading to un-appropriate use of ECMO.

Key Words: ARDS, Influenza A (H1N1), trans-pulmonary pressure, extracorporeal membrane oxygenation

INTRODUCTION

Several reports describe cases of *influenza* A (H1N1)-associated acute respiratory distress syndrome requiring extracorporeal membrane oxygenation (ECMO) for severe hypoxemia refractory to conventional treatment [1-6]. However, uncertainty regarding the appropriate indication for ECMO in these patients still remains [7-10]. Moreover, clinical evidences in support of ECMO as rescue treatment for these patients are controversial [11].

The increase in elastance of the respiratory system [12] observed in patients with ARDS is mainly attributed to the increase in elastance of the lung (E_L) [12]. Under these circumstances the elastic properties of the chest wall (E_{CW}) contributes to E_{RS} by approximately 20% [13]. However, alterations in E_{CW} have been described in patients with ARDS [13-15]. In these patients E_{CW} may contribute to E_{RS} up to 50% [16]. This implies that for a value of end-inspiratory plateau pressure of the respiratory system ($P_{PLAT_{RS}}$) of 30 cmH_2O, the end-inspiratory trans-pulmonary pressure (P_{PLAT_L}) will amount to 24 cmH_2O in patients with a "normal" chest wall and 15 cmH_2O in patients with a "stiff" chest wall [16]. This may be clinically relevant since: (***a***) several studies suggest that mechanical ventilation should be titrated on P_{PLAT_L} rather than on $P_{PLAT_{RS}}$; (***b***) it has been suggested that the upper physiological limit of trans-pulmonary pressure that optimizes alveolar recruitment is 25 cmH_2O [14, 15, 17].

We report a case-series of patients with *influenza* A (H1N1)-associated ARDS that were referred for ECMO but in whom assessment of trans-pulmonary pressure led

to a change of the ventilatory strategy that reversed refractory hypoxemia and avoided ECMO.

METHODS

We report patients with *influenza* A (H1N1)-associated ARDS referred to the Molinette Hospital (University of Turin) for ECMO in the period from September 2009 to January 2010 [18]. The institutional ethics committee approved data collection and report.

Patients were centralized if conventional ventilation [19], associated to nitric oxide, and/or prone positioning and/or high frequency oscillation resulted in: HbO_2<85%; oxygenation index>25; PaO_2/FiO_2<100 with PEEP≥10 cmH_2O; hypercapnia and respiratory acidosis with pH<7.25; SvO_2 or $SvcO_2$<65% despite Ht>30 and administration of vaso-active drugs [18]. Criteria for initiating ECMO were: oxygenation index>30; PaO_2/FiO_2<70 with PEEP≥15 cmH_2O; pH<7.25 for at least 2 hours [18]. Exclusion criteria for ECMO were: intracranial bleeding and other major contraindication to anticoagulation; previous severe disability; poor prognosis because of the underlying malignancy; mechanical ventilation for longer than 7 days [18].

At arrival, all patients were ventilated according to the ARDS Network protocol [19]. Mechanics of the respiratory system was partitioned between lung and chest wall. Throughout the period of data recording all patients were oro-tracheally intubated and in semi-recumbent position (head of bed from 30° to 45° inclination), sedated and paralyzed, as prescribed by the attending physicians.

Flow and $P_{PLAT_{RS}}$ were measured. The pressure required to distend the chest wall was estimated using the measurement of esophageal pressure (P_{ES}) [20]. E_{RS}, E_{CW}, and

E_L were calculated as previously described [20]. $P_{PLAT_{CW}}$ and end-inspiratory plateau pressure of the lung (P_{PLAT_L}) were estimated using the following equations [16]:

$$P_{PLAT_{CW}} = E_{CW} / E_{RS} * P_{PLAT_{RS}}$$

$$P_{PLAT_L} = P_{PLAT_{RS}} - P_{PLAT_{CW}}$$

Shape of the airway opening pressure vs. time during constant flow (*stress index*) was recorded as previously described [21-24].

If values of P_{PLAT_L} during conventional ventilation were <25 cmH_2O, PEEP was further increased until P_{PLAT_L} was equal to 25 cmH_2O [14, 15, 17]. ECMO criteria were hence evaluated 20-30 min after of ventilation with new PEEP setting. If values of P_{PLAT_L} during conventional ventilation were ≥25 cmH_2O, ECMO criteria were evaluated with ventilator settings as set on entry.

Data are presented as mean±standard deviation. Comparisons were performed using paired and unpaired T-test, as appropriate. Differences were considered significant if $P < 0.05$.

RESULTS

In the period October 2009-January 2010, 36 patients with novel A (H1N1) infection were admitted to the ICUs of the Piedmont region. Among them, 20 patients had ARDS and 14 were transferred to the regional coordinating center with ECMO facility because developing the pre-established criteria.

Values of oxygenation index and of PaO_2/FiO_2 ratio indicated immediate use of ECMO in all patients [18]. Partitioning of respiratory mechanics showed that in 7 patients P_{PLAT_L} was higher than 25 cmH_2O (27.2±1.2 cmH_2O) while in the other 7 patients was lower than 25 cmH_2O (16.6±2.9 cmH_2O) (**Table 1**). Values of $P_{PLAT_{RS}}$ were similar in the groups (31.0±1.0 vs. 31.5±0.5 cmH_2O, respectively). While in the former extracorporeal support was immediately initiated (***ECMO***), in the latter increasing PEEP until P_{PLAT_L} reached the upper physiological limit of trans-pulmonary pressure (25.3±1.7 cmH_2O) resulted in an increase of oxygenation index and of PaO_2/FiO_2 to an extent that criteria for extracorporeal support were no longer met and patients were treated with conventional ventilation associated to low-flow CO2 removal [25] in 4 patients (***NO ECMO***) (**Figure 1**).

Table 2 shows physiological parameters in the ***ECMO*** and in the ***NO ECMO*** group. Although values of E_{RS} did not differ, E_L was higher (32.3±5.3 vs. 20.2±4.7 cmH_2O/L; *P*=0.001) and E_{CW} was lower (6.1±0.7 vs. 17.2 ± 1.7; P=0.0001) in ***ECMO*** than in ***NO ECMO*** group. In the latter, increasing PEEP from 17.9±1.2 to 22.3±1.4 cmH_2O (P=0.0001) to target an increase in P_{PLAT_L} from 16.6±2.9 to 25.3±1.7 cmH_2O/L

(P=0.0001) significantly decreased the oxygenation index from 37±4 to 16±1 (P=0.0001). The significant (P=0.0001) increase of $P_{PLAT_{RS}}$ from 31.5±0.5 to 38.4±1.0 cmH_2O observed with conventional ventilation and higher PEEP was associated to: (a) the increase in E_{RS} (from 37.4±4.2to 43.8±3.3 cmH_2O/L; P=0.0001) and E_L (from 20.2±4.7 to 28.6±2.3 cmH_2O/L; P=0.0001); (b) the increase of *stress index* (from 0.922±0.033 to 1.052±0.032; P=0.0001); (c) the reduction in $PaCO_2$ (from 54.6±8.4 to 42.9±8.0; P=0.001). Increasing PEEP significantly increased right atrial pressure (from 17±2 to 20±3 mmHg, P=0.001) but did not affect mean systolic pressure, cardiac output and cardiac index.

Table 3 shows the clinical and demographic characteristics of the patients. Except for age (35.4±11.1 vs. 53.3±11.7 years; P=0.01) and fluid balance prior to admission to the referral center (718±270 vs. 1384±332 ml; P=0.01), Murray' score [26] (3.82±0.19 vs. 3.61±0.43) and other clinical variables did not differ between the ***ECMO*** and ***NO ECMO*** group.

DISCUSSION

The present case-series shows that partitioning of respiratory mechanics between lung and chest wall revealed a subset of patients with *influenza* A (H1N1)-associated ARDS in whom hypoxemia was refractory to the conventional treatment not because of a profound alteration of the lung parenchyma but because a large amount of the pressure applied at the airways was not transmitted to the lung parenchyma but dissipated against a "stiff" chest wall. In these patients, targeting PEEP to reach the upper physiological limit of trans-pulmonary pressure (25 cmH_2O) [14, 15, 17] instead of the "safe" limit of $P_{PLAT_{RS}}$ (30 cmH_2O) [19], improved oxygenation to an extent that ECMO criteria were no longer met.

The reported incidence of patients with influenza A (H1N1)-associated ARDS transitioning from conventional ventilation to ECMO is extremely variable. Reports from Australia and New Zealand [1] and from France [2] indicate that patients on ECMO were 34% and 50% of the mechanically ventilated patients, respectively. In Hong Kong [3] and Canada [4] only 6% of the patients were shifted from conventional ventilation to ECMO. In the present study, 14 patients were referred to the regional center to initiate ECMO for refractory hypoxemia. Partitioning of respiratory mechanics between lung and chest wall allowed to identify 7 patients that responded to conventional treatment and avoided ECMO provided that PEEP was sufficiently high to be transmitted to the collapsed lungs and to overcome chest wall stiffness. By doing so, the incidence of ECMO in the Piedmont region went from the possible 39% (14 on a

total of 36 mechanically ventilated patients) to the observed 19% (7 of the 36 mechanically ventilated patients) (Table 1).

Both in the ECMO and in the NO ECMO group the oxygenation index was equally compromised (Table 2) suggesting equal impairment of lung function. However, the oxygenation index is calculated using mean *airway* pressure. Indeed, the mean *transpulmonary* pressure during conventional mechanical ventilation was lower in ***NO ECMO*** than in the ***ECMO*** group (13.4±1.6 *versus* 21.4±1.7, P = 0.01) and therefore the oxygenation index calculated using the mean *transpulmonary* pressure was significantly lower in the ***NO ECMO*** than in the ***ECMO*** group (19.8±1.6 *versus* 28.7±4.8 P=0.01).

The "open lung" approach aims at maximizing alveolar recruitment and counteract tidal recruitment of unstable alveoli by setting PEEP as high as possible to match a $P_{PLAT_{RS}}$ of 30 cmH_2O [27-29]. A recent meta-analysis suggests that this approach may reduce mortality in patients with ARDS in comparison to the conventional approach [30]. Recently, Mercat and coworkers proposed an open lung protocol in which PEEP was individually set as high as possible to match an $P_{PLAT_{RS}}$ target of 30 cmH_2O [28]. The open lung strategy adopted in the present report is based on the same rationale but, in order to overcome the bias induced by chest wall stiffness, aimed at an end-inspiratory transpulmonary pressure of 25 cm cmH_2O. Of note this value is regarded as the he upper physiological limit of trans-pulmonary pressure [14, 15, 17] and is the value recorded in patients with ARDS and normal E_{CW} (E_{CW}/E_{RS} ratio

of 0.2) at a $P_{PLAT_{RS}}$ of 30 cmH_2O. This approach differs from the one proposed by Talmor and coworkers that titrated PEEP in order to obtain values of *end-expiratory* transpulmonary pressure ranging between 0 and 10 cmH_2O [20].

In patients with ARDS, the increase of E_{RS} is mainly attributed to E_L [31]. However, alterations in E_{CW} have been also described in these patients [13, 15]. Moreover, *influenza* A (H1N1)-associated ARDS frequently occurs in obese subjects [32], a category of patients that often present a compromised E_{CW} [33]. Under these circumstances: (a) part of $P_{PLAT_{RS}}$ may be "wasted" to distend the chest wall and only a fraction of the pressure applied at the airways will inflate the lung [14]; (b) the amount of pressure that will result in lung recruitment depends on the E_{CW}/E_{RS} ratio [16]. In normal adults the E_{CW}/E_{RS} ratio is approximately 0.4 [16]. In patients with ARDS, Gattinoni and coworkers [13] described patients with a normal chest wall and a E_{CW}/E_{RS} ratio of 0.2 and patients with a substantial impairment of the elastic properties of the chest wall and a E_{CW}/E_{RS} ratio of 0.5 [16]. Mergoni [34], Ranieri [15], and Grasso [14] later confirmed these findings. We show that in 7 of our patients, the impairment of the elastic properties of the respiratory system (E_{RS}=38.4±5.2 cmH_2O/L) was due to a profound and substantial alteration of the lung parenchyma. In these patients the E_{CW}/E_{RS} ratio was 0.16±0.03 and P_{PLAT_L} during conventional ventilation was 27.2±1.2 cmH_2O (**Table 2**). In these patients, hypoxemia was refractory to conventional treatments and ECMO was required to re-establish oxygenation. In the remaining patients, chest wall mechanics substantially contributed to the observed values of E_{RS} (37.4±4.2cmH_2O/L) with an E_{CW}/E_{RS} ratio of 0.47±0.08 (**Table 2**). In these patients,

during conventional ventilation and with a PEEP of 17.9±1.2 cmH_2O, baseline P_{PLAT_L} was 16.6±2.9 cmH_2O. Raising PEEP to 22.3±1.4 cmH_2O to target the upper physiological limit of P_{PLAT_L} (25.3±1.7 cmH_2O) decreased oxygenation index (from 37±4 to 16±1; P=0.0001) reverting the indication for ECMO and allowing treatment with conventional ventilation. The significant improvement in oxygenation (**Table 2**) with a relatively small increase of PEEP (4.4±1.4 cmH_2O, range 4 -6 cmH_2O) suggests a high potential for alveolar recruitment in the ***NO ECMO*** group [35].

Recent evidences [36] account for significant alveolar hyperinflation at $P_{PLAT_{RS}}$ levels higher than 28 cmH_2O. Several arguments support the lack of any direct or indirect evidence of hyperinflation observed in the present study even if we did not directly assess recruitment and hyperinflation. **First**, P_{PLAT_L} was significantly lower than $P_{PLAT_{RS}}$, due to high Est_{cw}. **Second**, *stress index* went from the range of values associated to tidal recruitment (0.922±0.033) to the range of values associated to protective ventilation (1.052 ± 0.032; P=0.0001). **Third,** although a decrease in cardiac output could have *per se* decreased shunt and improved oxygenation [37], we found that cardiac output remained unchanged. **Fourth**, the slight but significant increase of E_L with the higher PEEP strategy may be explained assuming that in these patients the increase of PEEP shifted tidal ventilation close to upper inflection point of the pulmonary volume-pressure curve [39-41] as also supported by recent evidence suggesting that “regional elastance” of lung tissue previously collapsed and re-expanded by applied pressure is higher than the elastance of the normally patent lung regions [42].

The observational nature of the present study limits the interpretation of its

results. ***First***, alterations of E_{CW} in patients with ARDS have been associated to excessive and unopposed abdominal pressure [43] or to pleural effusions due to a positive fluid balance [14]. Moreover, in normal subjects E_{RS} increases with age, due to an increase of E_{CW} [44]. Although we found that patients with an impaired chest wall mechanics were older (53.3±11.7 vs. 35.4±11.1 years; P=0.01) and had a more pronounced positive fluid balance (1384±332 vs.718±270 ml; P=0.01) than the patients that had a normal chest wall, the small number of patients included in study does not allow to identify clinical or physiological variables that could predict alteration of impairment of chest wall mechanics. ***Second,*** we report on a cohort of patients with a particularly diffuse and recruitable form of ARDS. ***Third***, portioning E_{RS} between E_{CW} and E_L is based on the measurement of P_{ES} and on the assumption that this measurement (***a***) represents the average pleural pressure [45], (***b***) is insensitive to changes in lung volume [46] and to local gradients in pleural pressure [12]. Unfortunately none of these assumptions have never been verified in patients with ARDS [47]. ***Fourth:*** Several other methods have been proposed to set up an open lung approach [48, 49]. Borges and coworkers showed that applying distending pressures up to 60 cmH_2O could successfully recruit the lung in ARDS patients considered not responders to conventional lung distending pressures [50]. Therefore it is conceivable that targeting a P_{PLAT_L} higher than 25 cmH_2O would have successfully recruited patients also in the ECMO group. Finally, we must point out that reducing tidal volume from 6 to 4 ml/Kg would have allowed higher PEEP levels at baseline in both groups [51].

May our data influence physicians' attitudes to implement ECMO in patients with ARDS? Unfortunately, available data come from case series [1-5, 18, 52] and only one randomized clinical trial tested the efficacy of ECMO in patients with severe ARDS [53]. **Table 4** presents the main ECMO criteria of these studies together with the ECMO criteria proposed by the Extracorporeal Life Support Organization guidelines [54]. As can be seen all our patients would have been treated with ECMO according to the existing criteria. Results of the present study may therefore suggest that (***a***) liberal and inclusive criteria for centralizing patients with H1N1-induced ARDS to center with ECMO facility [1-5, 18, 52] should not be considered "prima facie" grounds to actually implement ECMO; (***b***) titrating PEEP to target a P_{PLAT_L} value of 25 cmH_2O [14, 15, 17] instead of $P_{PLAT_{RS}}$ of 30 cmH_2O [27, 28] may optimize oxygenation and prevent un-appropriate use of ECMO in those patients with influenza A (H1N1)-associated ARDS that have an abnormal chest wall mechanics. Further studies are required to evaluate weather these conclusions may apply to a general population of ARDS patients.

FIGURE LEGENDS

Figure 1: Study flow chart. Definition of abbreviations: ARDS, acute respiratory distress syndrome; ECMO, extra-corporeal membrane oxygenation; PEEP, positive end-expiratory pressure; P_{PLAT_L}, trans-pulmonary pressure.

TABLE 1. Individual values of $P_{PLAT_{RS}}$ and P_{PLAT_L} **(cmH_2O)**

	ECMO			***NO ECMO***			
Patient initials	**CONVENTIONAL VENTILATION**		**Patient initials**	**CONVENTIONAL VENTILATION**		**CONVENTIONAL VENTILATION & HIGHER PEEP**	
	$P_{PLAT_{RS}}$	**P_{PLAT_L}**		**$P_{PLAT_{RS}}$**	**P_{PLAT_L}**	**$P_{PLAT_{RS}}$**	**P_{PLAT_L}**
BM	**32.1**	**28.5**	VV	**31.7**	**18.8**	**37.2**	**26.1**
DS	**29.7**	**25.8**	AR	**31.9**	**15.1**	**38.5**	**25.2**
CG	**31.3**	**25.6**	LR	**31.8**	**12.3**	**40.6**	**27.1**
FM	**30.4**	**27.6**	TV	**31.8**	**15.9**	**38.6**	**27.3**
BA	**30.8**	**26.9**	CG	**31**	**15.8**	**38**	**23.5**
EA	**31.2**	**28.8**	PS	**30.5**	**16.9**	**37.5**	**22.8**
TF	**31.4**	**27.2**	LF	**31.7**	**21.7**	**38.7**	**25**
Mean ± SD	**31 ± 1**	**27.2 ± 1.2**	**Mean ± SD**	**31 ± 0.5**	**16.6 ± 2.9**	**38.4 ± 1**	**25.3 ± 1.7**

Table 1; Definition of abbreviations: $P_{PLAT_{RS}}$ end-inspiratory plateau pressure of the respiratory system;
P_{PLAT_L}, end-inspiratory plateau pressure of the lung;
ECMO: extracorporeal membrane oxygenation; SD standard deviation

TABLE 2. Ventilatory, respiratory and gas exchange parameters.

	ECMO	*NO ECMO*	
	CONVENTIONAL VENTILATION	**CONVENTIONAL VENTILATION**	**CONVENTIONAL VENTILATION & HIGHER PEEP**
VT (ml/Kg PBW)	5.0±0.9	5.0±0.8	5.0±0.8
PEEP (cmH_2O)	17.1±1.6	17.9±1.2	22.3±1.4 #
RR (b/min)	32.8±2.4	31.1±0.3	30.3±2.4
Oxygenation Index	34±5	37±4	16±1 #
PaO_2/FiO_2	75±10	67±5	180±9 ##
$P_{AO, MEAN}$	25.2±2.7	25.1±1.8	29.1±1 #
$PaCO_2$ (mmHg)	54.3±7.4	54.6±8.4	42.9±8.0 ##
pH	7.386±0.035	7.371±0.094	7.405±0.089
$PPLAT_{RS}$ (cmH_2O)	31.0±1	31.5±0.5	38.4±1.0 #
$PPLAT_{CW}$ (cmH_2O)	4.0±1.4 *	14.7±2.5	13.5±0.8 #
$PPLAT_L$ (cmH_2O)	27.2±1.2 *	16.6±2.9	25.3±1.7 #
E_{RS} (cmH_2O/L)	38.4±5.2	37.4±4.2	43.8±3.3 #
E_L (cmH_2O/L)	32.3±5.3 **	20.2±4.7	28.6±2.3 #
E_{CW} (cmH_2O/L)	6.1±0.7 *	17.2±1.7	15.2 ± 2.6
E_{CW}/E_{RS}	0.16±0.03 *	0.47±0.08	0.35 ±0.04
Stress index	1.071±0.032	0.922±0.033	1.052±0.032 #

Definition of abbreviations: ECMO: extracorporeal membrane oxygenation; VT/Kg PBW, tidal volume/Kg predicted body weight; PEEP, positive end-expiratory pressure; RR, respiratory rate; PaO_2 = arterial partial pressure of O_2; FiO_2 inspired O_2 fraction; $\mathbf{P_{AO, MEAN}}$, mean airway opening pressure; $PaCO_2$ = arterial partial pressure of CO_2 ;; E_{RS} = static respiratory system elastance; E_L = static lung elastance; E_{CW} = static chest wall elastance. Data are expressed as mean ± standard deviation. $P = 0.0001$ $^{**}P = 0.001$ ECMO vs. NO ECMO;
$^{\#}P = 0.0001$ $^{\#\#}P = 0.001$ CONVENTIONAL VENTILATION vs. CONVENTIONAL VENTILATION &

TABLE 3. Demographic and clinical characteristics at admission to the referring center.

	Age	Gender	BMI	APACHE II	Murray's Score [26]	Co-morbidities	Rescue Therapies	Days of MV	Fluid balance (ml)	Outcome
ECMO	44	M	43	14	**3.75**	Obesity	PP, NO	3	456	A
	24	F	33	16	**4.00**	Obesity	PP, NO	0	827	A
	36	M	48	31	**3.50**	Obesity	PP, NO	1	1006	A
	34	M	31	22	**4.00**	Obesity	NO	4	474	D
	31	F	32	24	**4.00**	Obesity	PP	2	696	D
	24	M	23	9	**3.75**	None	NO	2	457	A
	55	M	22	19	**3.75**	None	PP, NO	1	1101	A
Mean	**35.4***		**33.2**	**19.3**	**3.82**			**1.9**	**718***	
SD	**11.1**		**9.5**	**7.2**	**0.19**			**1.3**	**270**	
NO ECMO	44	F	22	8	**3.75**	None	PP, NO	3	1342	A
	66	M	27	18	**3.75**	Diabetes	PP, NO	1	1120	A
	54	F	31	14	**3.00**	Obesity	PP, NO	4	1897	A
	38	F	24	8	**4.00**	Drug addiction	PP, NO	2	1254	A
	46	F	31	27	**3.00**	Obesity	PP, NO	5	1765	D
	55	M	37	23	**3.75**	Obesity	PP, NO	4	1326	A
	70	F	29	29	**4.00**	Diabetes	PP, NO	3	981	A
Mean	**53.3**		**28.7**	**18.1**	**3.61**			**3.1**	**1384**	
SD	**11.7**		**4.9**	**8.6**	**0.43**			**1.3**	**332**	

Definition of abbreviations: ECMO = extracorporeal membrane oxygenation; BMI = body mass index; APACHE II = Acute Physiology, Age and Chronic Health Evaluation II score; Rescue therapies: PP= prone position; NO = nitric oxide; Days of MV = days of mechanical ventilation prior admission to the referral center; A = alive; D = death; Fluid balance= cumulative fluid balance prior admission to the referral center

*** P=0.01 ECMO vs. NO ECMO**

TABLE 4. Main ECMO used in the present previous and previous studies.

	PREVIOUS CASE SERIES						GUIDELINES	CLINICAL TRIAL	TURIN CASE SERIES		
	Hong Kong [3]	Australia and New Zeland [1]	Canada [4]	Sweden [5]	Marseille South Hospital [2]	Italy [18]	ELSO [54]	CESAR[53]	ALL	ECMO	NO ECMO
Patients (n.)	7	61	6	13	9	49		90	14	7	7
Acute Lung Injury Score	3.8 [3.8-3.9]	3.8 [3.5-4.0]	N.A.	3.6 [3.3-4.0]	3.6 3.2-3.7]	3.7 [3.2-3.7]	3-4	3.5±0.6	3.7±0.3	3.8±0.2	3.6±0.4
Lowest PaO_2/FiO_2	56 [53-71]	56 [48-63]	58±17	83±11	52 [50-60]	61 [53-81]	< 80	76±30	70.8±7.4	74.6 ± 10.0	67.5 ± 4.5
Highest PEEP (cmH_2O)	16 [15-19]	18 [15-20]	20±0	17 [15-20]	12 [11-14]	15 [13-20]	n.a.	14±10	17.5±1.4	17.1±1.6	17.9±1.2
Highest Peak/End-Inspiratory Plateau pressure (cmH_2O)	34±5#	36 (33-38)#	44±42#	37 [31-38]#	31 [30-35]*	33 [30-35]*	> 30*	n.a.	31.2±0.8*	31.0±0.8*	31.5±0.5*

Definition of abbreviations: ECMO: extracorporeal membrane oxygenation; ELSO = extracorporeal life support organization; PaO_2 = arterial partial pressure of O_2; FiO_2 inspired O_2 fraction; PEEP, positive end-expiratory pressure.
Data are expressed as mean ± standard deviation or median and [interquartile range].
#Peak Pressure ; *End-Inspiratory plateau pressure

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