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ECMO CRITERIA FOR *INFLUENZA* A (H1N1) - ASSOCIATED ARDS: ROLE OF TRANSPULMONARY PRESSURE¹

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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_{PLATL}) close to its upper physiological limit (25 cmH₂O) 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_{PLATL} (25 cmH₂O).

Results: Fourteen patients were referred for ECMO. In 7 patients P_{PLATL} was 27.2 ± 1.2 cmH₂O; all these patients underwent ECMO. In the other 7 patients, P_{PLATL} was 16.6 ± 2.9 cmH₂O. Raising PEEP (from 17.9 ± 1.2 to 22.3 ± 1.4 cmH₂O, $P=0.0001$) to approach the upper physiological limit of trans-pulmonary pressure ($P_{PLATL}=25.3 \pm 1.7$ cmH₂O) 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_{PLATRS}). In these patients, titrating PEEP on P_{PLATRS} 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_{PLATRS}) of 30 cmH₂O, the end-inspiratory trans-pulmonary pressure (P_{PLATL}) will amount to 24 cmH₂O in patients with a “normal” chest wall and 15 cmH₂O 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_{PLATL} rather than on P_{PLATRS} ; (*b*) it has been suggested that the upper physiological limit of trans-pulmonary pressure that optimizes alveolar recruitment is 25 cmH₂O [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: $\text{HbO}_2 < 85\%$; oxygenation index > 25 ; $\text{PaO}_2/\text{FiO}_2 < 100$ with $\text{PEEP} \geq 10$ cmH_2O ; hypercapnia and respiratory acidosis with $\text{pH} < 7.25$; SvO_2 or $\text{SvcO}_2 < 65\%$ despite $\text{Ht} > 30$ and administration of vaso-active drugs [18]. Criteria for initiating ECMO were: oxygenation index > 30 ; $\text{PaO}_2/\text{FiO}_2 < 70$ with $\text{PEEP} \geq 15$ cmH_2O ; $\text{pH} < 7.25$ 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_{PLATRS} 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 cmH₂O, PEEP was further increased until P_{PLAT_L} was equal to 25 cmH₂O [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 cmH₂O, ECMO criteria were evaluated with ventilator settings as set on entry.

Data are presented as mean \pm 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 $\text{PaO}_2/\text{FiO}_2$ 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 cmH₂O (27.2 ± 1.2 cmH₂O) while in the other 7 patients was lower than 25 cmH₂O (16.6 ± 2.9 cmH₂O) (**Table 1**). Values of $\text{P}_{\text{PLAT}_{RS}}$ were similar in the groups (31.0 ± 1.0 vs. 31.5 ± 0.5 cmH₂O, 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 cmH₂O) resulted in an increase of oxygenation index and of $\text{PaO}_2/\text{FiO}_2$ 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 cmH₂O/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 cmH₂O ($P=0.0001$) to target an increase in P_{PLAT_L} from 16.6 ± 2.9 to 25.3 ± 1.7 cmH₂O/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_{PLATRS} 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 ± 4.2 to 43.8 ± 3.3 $\text{cmH}_2\text{O/L}$; $P=0.0001$) and E_{L} (from 20.2 ± 4.7 to 28.6 ± 2.3 $\text{cmH}_2\text{O/L}$; $P=0.0001$); (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 cmH₂O) [14, 15, 17] instead of the “safe” limit of P_{PLATRS} (30 cmH₂O) [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_{PLATRS} of 30 cmH₂O [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_{PLATRS} target of 30 cmH₂O [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 cmH₂O. 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_{PLATRS} of 30 cmH₂O. 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 cmH₂O [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_{PLATRS} 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 ($E_{RS}=38.4\pm 5.2$ cmH₂O/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_{PLATL} during conventional ventilation was 27.2 ± 1.2 cmH₂O (**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 ± 4.2 cmH₂O/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 cmH₂O, baseline P_{PLATL} was 16.6 ± 2.9 cmH₂O. Raising PEEP to 22.3 ± 1.4 cmH₂O to target the upper physiological limit of P_{PLATL} (25.3 ± 1.7 cmH₂O) 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 cmH₂O, range 4 -6 cmH₂O) suggests a high potential for alveolar recruitment in the *NO ECMO* group [35].

Recent evidences [36] account for significant alveolar hyperinflation at P_{PLATRS} levels higher than 28 cmH₂O. 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_{PLATL} was significantly lower than P_{PLATRS} , 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 cmH₂O 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 cmH₂O 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_{PLATL} value of 25 cmH₂O [14, 15, 17] instead of P_{PLATRS} of 30 cmH₂O [27, 28] may optimize oxygenation and prevent unappropriate 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 whether 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 PPLAT_{RS} and PPLAT_L (cmH₂O)

<i>ECMO</i>			<i>NO ECMO</i>				
Patient initials	CONVENTIONAL VENTILATION		Patient initials	CONVENTIONAL VENTILATION		CONVENTIONAL VENTILATION & HIGHER PEEP	
	PPLAT _{RS}	PPLAT _L		PPLAT _{RS}	PPLAT _L	PPLAT _{RS}	PPLAT _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: PPLAT_{RS} end-inspiratory plateau pressure of the respiratory system; PPLAT_L, end-inspiratory plateau pressure of the lung; ECMO: extracorporeal membrane oxygenation; SD standard deviation

TABLE 2. Ventilatory, respiratory and gas exchange parameters.

	<i>ECMO</i>		<i>NO ECMO</i>	
	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 (cmH₂O)	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 [#]
PaO₂/FiO₂	75±10		67±5	180±9 ^{##}
P_{AO, MEAN}	25.2±2.7		25.1±1.8	29.1±1 [#]
PaCO₂ (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} (cmH₂O)	31.0±1		31.5±0.5	38.4±1.0 [#]
PPLAT_{CW} (cmH₂O)	4.0±1.4 [*]		14.7±2.5	13.5±0.8 [#]
PPLAT_L (cmH₂O)	27.2±1.2 [*]		16.6±2.9	25.3±1.7 [#]
E_{RS} (cmH₂O/L)	38.4±5.2		37.4±4.2	43.8±3.3 [#]
E_L (cmH₂O/L)	32.3±5.3 ^{**}		20.2±4.7	28.6±2.3 [#]
E_{CW} (cmH₂O/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; PaO₂ = arterial partial pressure of O₂; FiO₂ inspired O₂ fraction; P_{AO, MEAN}, mean airway opening pressure; PaCO₂ = arterial partial pressure of CO₂; 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 ₂ O)	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 ₂ O)	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; PaO₂ = arterial partial pressure of O₂; FiO₂ inspired O₂ fraction; PEEP, positive end-expiratory pressure.

Data are expressed as mean ± standard deviation or median and [interquartile range].

#Peak Pressure ; *End-Inspiratory plateau pressure

REFERENCES

1. Davies A, Jones D, Bailey M, Beca J, Bellomo R, Blackwell N, Forrest P, Gattas D, Granger E, Herkes R, Jackson A, McGuinness S, Nair P, Pellegrino V, Pettila V, Plunkett B, Pye R, Torzillo P, Webb S, Wilson M, Ziegenfuss M, (2009) Extracorporeal Membrane Oxygenation for 2009 Influenza A(H1N1) Acute Respiratory Distress Syndrome. *JAMA* 302: 1888-1895
2. Roch A, Lepaul-Ercole R, Grisoli D, Bessereau J, Brissy O, Castanier M, Dizier S, Forel JM, Guervilly C, Gariboldi V, Collart F, Michelet P, Perrin G, Charrel R, Papazian L, Extracorporeal membrane oxygenation for severe influenza A (H1N1) acute respiratory distress syndrome: a prospective observational comparative study. *Intensive care medicine* 36: 1899-1905
3. Chan KK, Lee KL, Lam PK, Law KI, Joynt GM, Yan WW, (2010) Hong Kong's experience on the use of extracorporeal membrane oxygenation for the treatment of influenza A (H1N1). *Hong Kong medical journal = Xianggang yi xue za zhi / Hong Kong Academy of Medicine* 16: 447-454
4. Freed DH, Henzler D, White CW, Fowler R, Zarychanski R, Hutchison J, Arora RC, Manji RA, Legare JF, Drews T, Veroukis S, Kesselman M, Guerguerian AM, Kumar A, (2010) Extracorporeal lung support for patients who had severe respiratory failure secondary to influenza A (H1N1) 2009 infection in Canada. *Canadian journal of anaesthesia = Journal canadien d'anesthésie* 57: 240-247
5. Holzgraefe B, Broome M, Kalzen H, Konrad D, Palmer K, Frenckner B, (2010) Extracorporeal membrane oxygenation for pandemic H1N1 2009 respiratory failure. *Minerva Anestesiologica* 76: 1043-1051
6. Noah MA, Peek GJ, Finney SJ, Griffiths MJ, Harrison DA, Grieve R, Sadique MZ, Sekhon JS, McAuley DF, Firmin RK, Harvey C, Cordingley JJ, Price S, Vuylsteke A, Jenkins DP, Noble DW, Bloomfield R, Walsh TS, Perkins GD, Menon D, Taylor BL, Rowan KM, (2011) Referral to an Extracorporeal Membrane Oxygenation Center and Mortality Among Patients With Severe 2009 Influenza A(H1N1). *JAMA*
7. Dalton HJ, MacLaren G, (2010) Extracorporeal membrane oxygenation in pandemic flu: insufficient evidence or worth the effort? *Crit Care Med* 38: 1484-1485
8. Hubmayr RD, Farmer JC, (2010) Should we "rescue" patients with 2009 influenza A(H1N1) and lung injury from conventional mechanical ventilation? *Chest* 137: 745-747
9. Morris AH, Hirshberg E, Miller RR, 3rd, Statler KD, Hite RD, (2010) Counterpoint: Efficacy of extracorporeal membrane oxygenation in 2009 influenza A(H1N1): sufficient evidence? *Chest* 138: 778-781; discussion 782-774
10. Park PK, Dalton HJ, Bartlett RH, (2010) Point: Efficacy of extracorporeal membrane oxygenation in 2009 influenza A(H1N1): sufficient evidence? *Chest* 138: 776-778
11. Mitchell MD, Mikkelsen ME, Umscheid CA, Lee I, Fuchs BD, Halpern SD, (2010) A systematic review to inform institutional decisions about the use of

- extracorporeal membrane oxygenation during the H1N1 influenza pandemic. *Crit Care Med* 38: 1398-1404
12. Hubmayr RD, Rodarte JR, Walters BJ, Tonelli FM, (1987) Regional ventilation during spontaneous breathing and mechanical ventilation in dogs. *Journal of applied physiology: respiratory, environmental and exercise physiology* 63: 2467-2475
 13. Gattinoni L, Pelosi P, Suter PM, Pedoto A, Vercesi P, Lissoni A, (1998) Acute respiratory distress syndrome caused by pulmonary and extrapulmonary disease. Different syndromes? *Am J Respir Crit Care Med* 158: 3-11
 14. Grasso S, Mascia L, Del Turco M, Malacarne P, Giunta F, Brochard L, Slutsky AS, Marco Ranieri V, (2002) Effects of recruiting maneuvers in patients with acute respiratory distress syndrome ventilated with protective ventilatory strategy. *Anesthesiology* 96: 795-802
 15. Ranieri VM, Brienza N, Santostasi S, Puntillo F, Mascia L, Vitale N, Giuliani R, Memeo V, Bruno F, Fiore T, Brienza A, Slutsky AS, (1997) Impairment of lung and chest wall mechanics in patients with acute respiratory distress syndrome: role of abdominal distension. *Am J Respir Crit Care Med* 156: 1082-1091
 16. Gattinoni L, Chiumello D, Carlesso E, Valenza F, (2004) Bench-to-bedside review: chest wall elastance in acute lung injury/acute respiratory distress syndrome patients. *Crit Care* 8: 350-355
 17. Colebatch HJ, Greaves IA, Ng CK, (1979) Exponential analysis of elastic recoil and aging in healthy males and females. *Journal of applied physiology: respiratory, environmental and exercise physiology* 47: 683-691
 18. Patroniti N, Zangrillo A, Pappalardo F, Peris A, Cianchi G, Braschi A, Iotti GA, Arcadipane A, Panarello G, Ranieri VM, Terragni P, Antonelli M, Gattinoni L, Oleari F, Pesenti A, (2011) The Italian ECMO network experience during the 2009 influenza A(H1N1) pandemic: preparation for severe respiratory emergency outbreaks. *Intensive care medicine* 37: 1447-1457
 19. The Acute Respiratory Distress Network (2000) Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *N Engl J Med* 342: 1301-1308
 20. Talmor D, Sarge T, Malhotra A, O'Donnell CR, Ritz R, Lisbon A, Novack V, Loring SH, (2008) Mechanical ventilation guided by esophageal pressure in acute lung injury. *N Engl J Med* 359: 2095-2104
 21. Ranieri VM, Giuliani R, Fiore T, Dambrosio M, Milic-Emili J, (1994) Volume-pressure curve of the respiratory system predicts effects of PEEP in ARDS: "occlusion" versus "constant flow" technique. *AmJRespirCrit Care Med* 149: 19-27
 22. Ranieri VM, Zhang H, Mascia L, Aubin M, Lin CY, Mullen JB, Grasso S, Binnie M, Volgyesi GA, Eng P, Slutsky AS, (2000) Pressure-time curve predicts minimally injurious ventilatory strategy in an isolated rat lung model. *Anesthesiology* 93: 1320-1328

23. Grasso S, Stripoli T, De Michele M, Bruno F, Moschetta M, Angelelli G, Munno I, Ruggiero V, Anaclerio R, Cafarelli A, Driessen B, Fiore T, (2007) ARDSnet ventilatory protocol and alveolar hyperinflation: role of positive end-expiratory pressure. *Am J Respir Crit Care Med* 176: 761-767
24. Grasso S, Terragni P, Mascia L, Fanelli V, Quintel M, Herrmann P, Hedenstierna G, Slutsky AS, Ranieri VM, (2004) Airway pressure-time curve profile (stress index) detects tidal recruitment/hyperinflation in experimental acute lung injury. *Crit Care Med* 32: 1018-1027
25. Terragni PP, Del Sorbo L, Mascia L, Urbino R, Martin EL, Birocco A, Faggiano C, Quintel M, Gattinoni L, Ranieri VM, (2009) Tidal volume lower than 6 ml/kg enhances lung protection: role of extracorporeal carbon dioxide removal. *Anesthesiology* 111: 826-835
26. Murray JF, Matthay MA, Luce JM, Flick MR, (1988) An expanded definition of the adult respiratory distress syndrome. *The American review of respiratory disease* 138: 720-723
27. Brower RG, Lanken PN, MacIntyre N, Matthay MA, Morris A, Ancukiewicz M, Schoenfeld D, Thompson BT, (2004) Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. *N Engl J Med* 351: 327-336
28. Mercat A, Richard JC, Vielle B, Jaber S, Osman D, Diehl JL, Lefrant JY, Prat G, Richecoeur J, Nieszkowska A, Gervais C, Baudot J, Bouadma L, Brochard L, (2008) Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 299: 646-655
29. Meade MO, Cook DJ, Guyatt GH, Slutsky AS, Arabi YM, Cooper DJ, Davies AR, Hand LE, Zhou Q, Thabane L, Austin P, Lapinsky S, Baxter A, Russell J, Skrobik Y, Ronco JJ, Stewart TE, (2008) Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 299: 637-645
30. Briel M, Meade M, Mercat A, Brower RG, Talmor D, Walter SD, Slutsky AS, Pullenayegum E, Zhou Q, Cook D, Brochard L, Richard JC, Lamontagne F, Bhatnagar N, Stewart TE, Guyatt G, (2010) Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis. *JAMA* 303: 865-873
31. Brander L, Ranieri VM, Slutsky AS, (2006) Esophageal and transpulmonary pressure help optimize mechanical ventilation in patients with acute lung injury. *Crit Care Med* 34: 1556-1558
32. Fezeu L, Julia C, Henegar A, Bitu J, Hu FB, Grobbee DE, Kengne AP, Herberg S, Czernichow S, (2011) Obesity is associated with higher risk of intensive care unit admission and death in influenza A (H1N1) patients: a systematic review and meta-analysis. *Obes Rev*
33. Salome CM, King GG, Berend N, (2010) Physiology of obesity and effects on lung function. *Journal of applied physiology: respiratory, environmental and exercise physiology* 108: 206-211
34. Mergoni M, Martelli A, Volpi A, Primavera S, Zuccoli P, Rossi A, (1997) Impact of positive end-expiratory pressure on chest wall and lung pressure-

- volume curve in acute respiratory failure. *Am J Respir Crit Care Med* 156: 846-854
35. Fan E, Wilcox ME, Brower RG, Stewart TE, Mehta S, Lapinsky SE, Meade MO, Ferguson ND, (2008) Recruitment maneuvers for acute lung injury: a systematic review. *Am J Respir Crit Care Med* 178: 1156-1163
 36. Terragni PP, Rosboch G, Tealdi A, Corno E, Menaldo E, Davini O, Gandini G, Herrmann P, Mascia L, Quintel M, Slutsky AS, Gattinoni L, Ranieri VM, (2007) Tidal hyperinflation during low tidal volume ventilation in acute respiratory distress syndrome. *Am J Respir Crit Care Med* 175: 160-166
 37. Matamis D, Lemaire F, Harf A, Teisseire B, Brun-Buisson C, (1984) Redistribution of pulmonary blood flow induced by positive end-expiratory pressure and dopamine infusion in acute respiratory failure. *The American review of respiratory disease* 129: 39-44
 38. Ranieri VM, Giuliani R, Cinnella G, Pesce C, Brienza N, Ippolito EL, Pomo V, Fiore T, Gottfried SB, Brienza A, (1993) Physiologic effects of positive end-expiratory pressure in patients with chronic obstructive pulmonary disease during acute ventilatory failure and controlled mechanical ventilation. *The American review of respiratory disease* 147: 5-13
 39. Maggiore SM, Jonson B, Richard JC, Jaber S, Lemaire F, Brochard L, (2001) Alveolar derecruitment at decremental positive end-expiratory pressure levels in acute lung injury: comparison with the lower inflection point, oxygenation, and compliance. *Am J Respir Crit Care Med* 164: 795-801
 40. Jonson B, Richard JC, Straus C, Mancebo J, Lemaire F, Brochard L, (1999) Pressure-volume curves and compliance in acute lung injury: evidence of recruitment above the lower inflection point. *Am J Respir Crit Care Med* 159: 1172-1178
 41. Richard JC, Brochard L, Vandelet P, Breton L, Maggiore SM, Jonson B, Clabault K, Leroy J, Bonmarchand G, (2003) Respective effects of end-expiratory and end-inspiratory pressures on alveolar recruitment in acute lung injury. *Crit Care Med* 31: 89-92
 42. Grasso S, Stripoli T, Sacchi M, Trerotoli P, Staffieri F, Franchini D, De Monte V, Valentini V, Pugliese P, Crovace A, Driessen B, Fiore T, (2009) Inhomogeneity of lung parenchyma during the open lung strategy: a computed tomography scan study. *Am J Respir Crit Care Med* 180: 415-423
 43. Hess DR, Bigatello LM, (2008) The chest wall in acute lung injury/acute respiratory distress syndrome. *Current opinion in critical care* 14: 94-102
 44. Frank NR, Mead J, Ferris BG, Jr., (1957) The mechanical behavior of the lungs in healthy elderly persons. *The Journal of clinical investigation* 36: 1680-1687
 45. Milic-Emili J, Mead J, Turner JM, Glauser EM, (1964) Improved Technique for Estimating Pleural Pressure from Esophageal Balloons. *Journal of applied physiology: respiratory, environmental and exercise physiology* 19: 207-211
 46. Rehder K, Abboud N, Rodarte JR, Hyatt RE, (1975) Positive airway pressure and vertical transpulmonary pressure gradient in man. *Journal of applied physiology: respiratory, environmental and exercise physiology* 38: 896-899

47. Hubmayr RD, (2010) Is there a place for esophageal manometry in the care of patients with injured lungs? *Journal of applied physiology: respiratory, environmental and exercise physiology* 108: 481-482
48. Suarez-Sipmann F, Bohm SH, Tusman G, Pesch T, Thamm O, Reissmann H, Reske A, Magnusson A, Hedenstierna G, (2007) Use of dynamic compliance for open lung positive end-expiratory pressure titration in an experimental study. *Crit Care Med* 35: 214-221
49. Hodgson CL, Tuxen DV, Davies AR, Bailey MJ, Higgins AM, Holland AE, Keating JL, Pilcher D, Westbrook AJ, Cooper DJ, Nichol A, (2011) A randomised controlled trial of an open lung strategy with staircase recruitment, titrated PEEP and targeted low airway pressures in patients with acute respiratory distress syndrome. *Crit Care* 15: R133
50. Borges JB, Okamoto VN, Matos GF, Caramez MP, Arantes PR, Barros F, Souza CE, Victorino JA, Kacmarek RM, Barbas CS, Carvalho CR, Amato MB, (2006) Reversibility of lung collapse and hypoxemia in early acute respiratory distress syndrome. *Am J Respir Crit Care Med* 174: 268-278
51. Hager DN, Krishnan JA, Hayden DL, Brower RG, (2005) Tidal volume reduction in patients with acute lung injury when plateau pressures are not high. *Am J Respir Crit Care Med* 172: 1241-1245
52. Norfolk SG, Hollingsworth CL, Wolfe CR, Govert JA, Que LG, Cheifetz IM, Hollingsworth JW, (2010) Rescue therapy in adult and pediatric patients with pH1N1 influenza infection: a tertiary center intensive care unit experience from April to October 2009. *Crit Care Med* 38: 2103-2107
53. Peek GJ, Mugford M, Tiruvoipati R, Wilson A, Allen E, Thalanany MM, Hibbert CL, Truesdale A, Clemens F, Cooper N, Firmin RK, Elbourne D, (2009) Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. *Lancet* 374: 1351-1363
54. (ELSO) ELSO (2009) Extracorporeal Life Support Organization (ELSO) Guidelines. In: Editor (ed)^(eds) Book Extracorporeal Life Support Organization (ELSO) Guidelines. City, pp.