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Impact of positive end-expiratory pressure on the definition of acute respiratory distress syndrome

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Abstract *Objective:* We examined whether PEEP during the first hours of ARDS can induce such a change in oxygenation that could mask fulfillment of the AECC criteria of a $PaO_2/FIO_2 \leq 200$ essential for ARDS diagnosis. *Design and setting:* Observational, prospective cohort in two medical-surgical ICU in teaching hospitals. *Patients:* 48 consecutive patients who met AECC criteria of ARDS on 0 PEEP (ZEEP) at the moment of diagnosis. *Measurements and results:* PaO_2/FIO_2 and lung mechanics were recorded on admission (0 h) to the ICU on ZEEP, and after 6, 12, and 24 h on PEEP levels selected by attending physicians. Lung Injury Score (LIS) was calculated at 0 and 24 h. PaO_2/FIO_2 rose significantly from 121±45 on ZEEP at 0 h, to 234±85 on PEEP of 12.8±3.7 cmH_2O after 24 h. LIS did not change significantly (2.34±0.53 vs. 2.42±0.62). These variables behaved similarly in pulmonary and extrapulmonary ARDS, and in survivors and nonsurvivors. After 24 h only 18 patients (38%) still had a PaO_2/FIO_2 of 200 or lower. Their mortality was similar to that in the remaining patients (61% vs. 53%). *Conclusions:* The use of PEEP improved oxygenation such that one-half of patients after 6 h, and most after 24 h did not fulfill AECC hypoxemia criteria of ARDS. However, LIS remained stable in the overall series. These results suggest that PEEP level should be taken into consideration for ARDS diagnosis.

Keywords Acute lung injury · Acute respiratory distress syndrome · Hypoxemia · Diagnosis · Positive end-expiratory pressure · Mechanical ventilation

Introduction

In 1967 Ashbaugh et al. [1] described the adult respiratory distress syndrome (ARDS) as a pulmonary noncardiogenic edema causing acute respiratory failure, bilateral infiltrates on chest radiography (CXR), deep hypoxemia, and diminished compliance (see also [2]. Subsequent descriptions showed great variability in the oxygenation criteria required for diagnosis [3, 4, 5, 6], and this precluded comparison of incidences, risk factors, mortality, and, especially, responses to therapy.

The first attempt to homogenize preexistent definitions and to establish a grading of severity was the introduction of the Lung Injury Score (LIS) [7, 8, 9, 10, 11]. This quantifies the three usual criteria for ARDS diagnosis and adds the use of positive end-expiratory pressure (PEEP). For the first time, a measure of a therapeutic maneuver was considered in the definition, although criticisms for adding further variability arose [12].

The American-European Consensus Conference (AECC) subsequently defined ARDS as an acute-onset respiratory failure, with bilateral infiltrates on CXR and PaO_2/FIO_2 of 200 or lower, irrespective of PEEP level, and absence of left ventricular failure [13]. Acute lung injury (ALI) was defined similarly but with less oxygenation deficit.

Although widely adopted, the AECC definition generated some criticism, referring to the division in ALI/ARDS [14], the inability to reflect its actual severity [15], its lack of standardization of infiltrates on CXR [16, 17], and even for ignoring inflammation variables [18]. In addition, the oxygenation criterion may be markedly modified by therapeutic measures already present at the moment of ARDS diagnosis, but not considered in AECC definition, such as PEEP level. Some investigators have suggested the consideration of PEEP in ARDS definition, to more accurately estimate oxygenation derangement [14, 15].

Our hypothesis was that optimization of respiratory variables in the first hours after ARDS diagnosis induces such change in PaO_2/FIO_2 that could mask the fulfillment of the AECC criteria already present at ICU admission. We also sought to determine the extent of the change in the PaO_2/FIO_2 ratio in pulmonary and extrapulmonary ARDS, and in survivors and nonsurvivors. Finally, we looked for differences between patients who remained as ARDS after 24 h and those who progressed to ALI.

Materials and methods

We studied consecutive patients between 1 July 2001 and 1 February 2002 with acute respiratory failure on admission to the ICU, newly intubated and on mechanical ventilation, which fulfilled AECC criteria of ARDS. All patients were ventilated with tidal volumes in the range of 5–6 ml/kg unless there were contraindications for hypercapnia, and plateau pressures were kept under 30 cmH_2O), according to protective ventilatory strategies recently developed [9, 19, 20]. The study was approved by the respective institutional boards. Informed consent was waived because measurements were considered as part of the general management of patients, and no special intervention was performed.

Patients were first assessed at a PEEP level of 0 cmH_2O (ZEEP) and had not been on any level of PEEP previously. An inspired oxygen fraction (FIO_2) that could keep pulse oxygen saturation higher than 90% on ZEEP was set. Then arterial blood gases were drawn and CXR was performed. Respiratory variables recorded were tidal volume (Vt; ml/kg of actual body weight), peak, plateau and mean pressures (cmH_2O), and total respiratory system (static) compliance (ml/cmH_2O). Plateau pressure was measured during a 2-s end-inspiratory pause with microprocessed ventilators. All these measurements were carried out in less than 30 min. Thereafter, PEEP was increased according to the criteria of the attending physician. There was no intention to titrate PEEP in a predetermined fashion, since there is no agreement on the best approach to do so. For the same reason, recruitment maneuvers were not performed before PEEP application. Blood gases and compliance measurements were repeated after 6, 12, and 24 h with the PEEP level that had been selected by the attending physician. CXR was repeated at 24 h. All CXR were independently assessed by two investigators. Any disagreement was solved by consensus with the aid of a third investigator. PaO_2/FIO_2 relationship was calculated at 0, 6, 12, and 24 h LIS was calculated only at 0 and 24 h because it was felt that a four-time exposure to radiography only for study purposes would be unethical. Severity of illness on admission was assessed by Acute Physiology and Chronic Health Evaluation II (APACHE II) and Sequential Organ Failure Assessment (SOFA) scores. Risk factors for ARDS were recorded as pulmonary or extrapulmonary. Patients with pneumonia and septic shock were considered as ARDS of pulmonary cause. Hospital mortality was recorded.

Data were analyzed in the overall series and was compared in the following groups: ARDS of pulmonary cause (ARDS-P) vs. extrapulmonary cause (ARDS-EP) and survivors vs. nonsurvivors. Additionally, different responses to PEEP after 24 h defined two groups. Patients who remained with PaO_2/FIO_2 of 200 or lower were considered as $ARDS_{24\text{-}h}$, and those who after 24 h had improved their PaO_2/FIO_2 to levels higher than 200 were considered as $ALI_{24\text{-}h}$. Organ failures on admission and after 24 h, and the outcomes of these two groups were also assessed.

Continuous data of normal distribution are presented as mean ±standard deviation (SD) and were analyzed by repeated-measurements analysis of variance and paired *t* test with Bonferroni's correction for the overall series and by two-way analysis of variance and unpaired *t* test with Bonferroni's correction for subgroup comparisons. Discrete variables were analyzed by the χ^2 test. The level of $p<0.05$ was considered as statistically significant. Statistical analysis was performed with Stata 6.0 software (Stata, Texas, USA).

Results

Forty-eight patients were included in the study. One-half of the patients had pulmonary causes of ARDS. The most frequent risk factor was pneumonia (50%). In the 24 patients with extrapulmonary ARDS, septic shock was the most common cause (42%). Mortality in the overall series was 56% (27/48). Table 1 presents the clinical characteristics of the $ARDS_{24\text{-}h}$ and $ALI_{24\text{-}h}$ groups, and Table 2, the mechanical ventilation displays parameters.

Table 1 Characteristics of the overall series and of the $ARDS_{24\text{-}h}$ and $ALI_{24\text{-}h}$ groups (*APACHE* Acute Physiology and Chronic Health Evaluation, *LIS* Lung Injury Score, *SOFA* Sequential Organ Failure Assessment)

	Overall (*n*=48)	$ARDS_{24\text{-}h}$ (*n*=18)	$ALI_{24\text{-}h}$ (*n*=30)	*p*
Age	46±19	45±16	47±22	0.74
APACHE II	23±8	23±6	24±8	0.70
ARDS of pulmonary cause	24 (50%)	9 (50%)	15 (50%)	1.00
LIS (admission)	2.34±0.53	2.27±0.63	2.38±0.47	0.52
LIS (24 h)	2.42±0.62	2.74±0.70*	2.24±0.50	0.007
SOFA score (admission)	9±3	9±3	9±3	0.98
SOFA score (24 h)	8±3	9±3	7±3[a]	0.38
Mortality	27 (56%)	11 (61%)	16 (53%)	0.78

*$p<0.01$ vs. admission

Table 2 Mechanical ventilation parameters and lung mechanics in the overall series and of $ARDS_{24\text{-}h}$ and $ALI_{24\text{-}h}$ groups on admission

	Overall (n=48)	$ARDS_{24\text{-}h}$ (n=18)	$ALI_{24\text{-}h}$ (n=30)	p
Tidal volume (ml/kg)	6.7±1.5	6.2±1.3	6.9±1.5	0.30
FIO_2	0.79±0.25	0.75±0.24	0.81±0.25	0.45
Peak pressure (cmH_2O)	29.6±10.5	31.4±10.2	28.4±10.7	0.36
Plateau pressure (cmH_2O)	21.2±7.8	22.9±7.1	20.4±8.0	0.35
Mean pressure (cmH_2O)	9.8±6.5	9.3±6.6	10.1±6.6	0.78
Static compliance (ml/cmH_2O)	26.0±10.0	23.8±9.7	31.0±8.4	0.17

Table 3 Course of physiological variables in the overall series

	0 h	6 h	12 h	24 h
PaO_2/FIO_2	121±45	203±75*	222±79*	234±85*
FIO_2	0.79±0.25	0.57±0.17	0.48±0.12	0.50±0.19*
Respiratory rate (breaths/min)	21±5	21±4	22±4	21±4
PEEP (cmH_2O)	0	11.5±4.3*	11.7±4.3*	12.8±3.7*
$PEEP_{intrinsic}$ (cmH_2O)	0.9±2.0	0.8±1.6	0.9±1.5	0.7±1.1
Static compliance (ml/cmH_2O)	26±10	37±12*	41±18[a]	41±16[a]
CXR (no. of quadrants)	3.0±1.2	–	–	3.1±1.0
LIS	2.34±0.53	–	–	2.42±0.62

*[a] $p<0.0001$ vs. 0 h

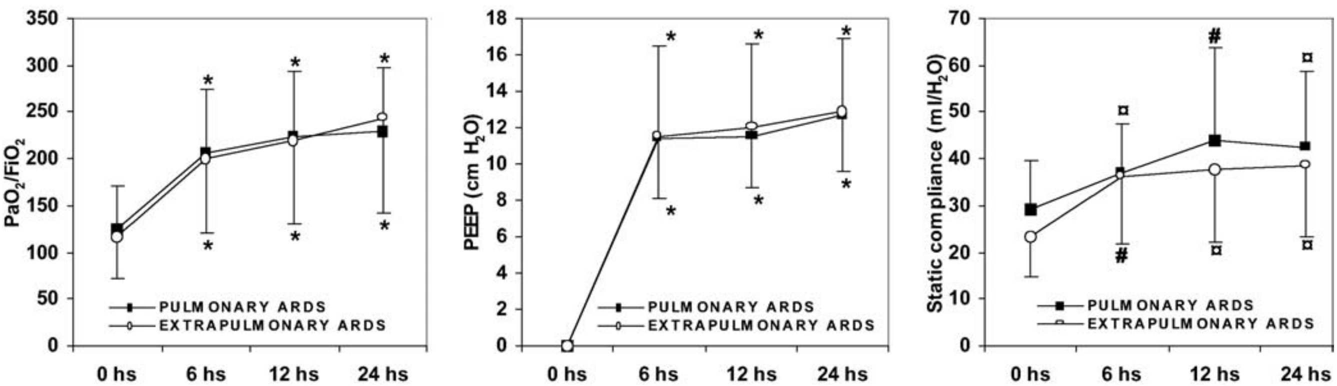

Fig. 1 PaO_2/FIO_2, PEEP and static respiratory system compliance in ARDS of pulmonary (closed *squares*) and extrapulmonary causes (*open circles*) on admission and after 6, 12, and 24 h. #$p<0.05$ vs. basal, $p<0.01$ vs. basal, *$p<0.0001$ vs. basal

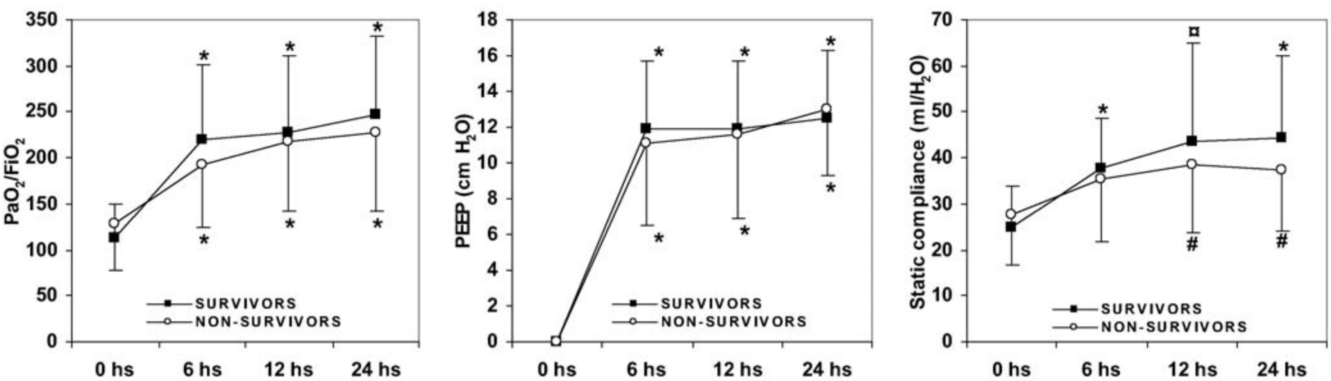

Fig. 2 PaO_2/FIO_2, PEEP and static respiratory system compliance in ARDS survivors (*closed squares*) and nonsurvivors (*open circles*) on admission and after 6, 12, and 24 h. #$p<0.05$ vs. basal, $p<0.01$ vs. basal, *$p<0.0001$ vs. basal

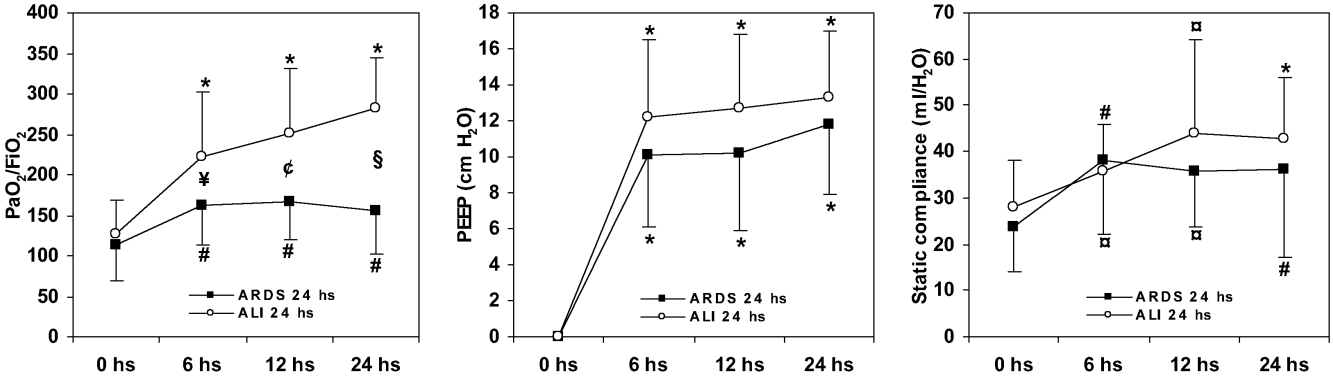

Fig. 3 PaO_2/FIO_2, PEEP, and static respiratory system compliance in $ARDS_{24\text{-h}}$ (*closed squares*) and $ALI_{24\text{-h}}$ (*open circles*) on admission and after 6, 12, and 24 h. $^{\#}p<0.05$ vs. basal, $p<0.01$ vs. basal, $^{*}p<0.0001$ vs. basal, $^{¥}p<0.05$ vs. the other group, $^{¢}p<0.001$ vs. the other group, $^{§}p<0.0001$ vs. the other group

Table 3 shows the changes in physiological variables that compounded LIS in the first 24 h after diagnosis in the overall series plus the level of applied FIO_2. The opinion of a third investigator for the evaluation of the CXR was required in seven cases (15% of patients). The use of PEEP was associated with a significant improvement in oxygenation, already present at 6 h. Respiratory system compliance also changed significantly after 6 h. However, LIS remained stable. The response of PaO_2/FIO_2, compliance, and LIS to increments of PEEP was similar in ARDS-P and ARDS-EP groups (Fig. 1) and in survivors and nonsurvivors (Fig. 2) to the overall series.

After 6 and 12 h, 25 patients (52%) no longer fulfilled the AECC criteria for ARDS. After 24 h 30 patients (62%) showed a PaO_2/FIO_2 higher than 200 ($ALI_{24\text{-h}}$) without LIS changes. In the remaining 18 patients, (38%) who still maintained a PaO_2/FIO_2 of 200 or lower ($ARDS_{24\text{-h}}$), LIS increased significantly ($p<0.01$). PaO_2/FIO_2 at 0 h did not differ between the two groups, but improvement in oxygenation was less in the $ARDS_{24\text{-h}}$ group, notwithstanding similar PEEP levels (Fig. 3). The $ALI_{24\text{-h}}$ group had a tendency towards a lower mortality (53% vs. 61%), and organ failures significantly improved after 24 h

Discussion

ARDS is usually diagnosed at a particular moment in the patient's course. However, clinical and physiological variables used as diagnostic criteria [7, 13] may be greatly modified by the course of ARDS or by effects of therapeutic measures. Few studies evaluate the temporal behavior of diagnostic variables [21]. Our hypothesis was that increasing PEEP levels, the mainstay of the treatment of hypoxemia, could mask the presence of ARDS because of elevations in the PaO_2/FIO_2 ratio.

In our patients, the use of PEEP enhanced arterial oxygenation, and therefore 6 h after diagnosis 52% of patients no longer fulfilled the oxygenation criteria of the AECC definition. After 24 h most patients (62%) were in the same condition. As no recruitment maneuvers were performed, we ascribe oxygenation improvement mainly to PEEP. Had patients been evaluated 6 h after admission to the protocol, more than one-half would have been misclassified as having ALI, a less severe syndrome. This could be a common situation, since oxygenation in critically ill patients may be assessed for the first time with some level of PEEP due to desaturation on pulse oxymetry and delays in blood gases extraction. Alternatively, patients may be transferred to reference centers already on PEEP. Concerns with derecruitment would make the decrease in PEEP unadvisable.

The AECC defines an arbitrary cutoff PaO_2/FIO_2 point of 200 between ARDS and ALI, as these conditions may represent a continuum of severity of the same entity. AECC investigators have speculated that a majority of patients with PaO_2/FIO_2 lower than 250 would eventually fulfill ARDS criteria [4, 13]. Luhr et al. [10] found that only 2.3% of ALI patients developed ARDS, but Bersten et al. [11] observed that 67% of ALI patients progress to ARDS. Therefore the progression from ALI to ARDS, probably due to worsening of the primary illness, is well documented. In contrast to the cited reports, most patients in our study changed their diagnostic category in the opposite direction, from ARDS to ALI, consequent to the increment of PEEP and notwithstanding the expected worsening during the first hours. There are references to possible misclassifications due to improvement ine oxygenation that could reverse ALI and/or ARDS, caused by therapeutic measurements as extracorporeal membrane oxygenation, inhaled nitric oxide, or prone positioning [10], but there is no report to the response to PEEP. Recruitment maneuvers could also act on this direction. Factors promoting alveolar derecruitment (ventilator disconnections, tracheal suctioning) may also modify oxygenation. In addition, cardiac output improvement can generate opposite changes on arterial PO_2 depending on the relative weight of increased shunt vs. increased mixed venous PO_2 [22].

The discrimination between ALI and ARDS in terms of prognosis is another controversial issue. Some investigators have found similar mortality in the two syndromes [10, 23], but others describe a worse outcome for ARDS: mortality of 60% vs. 31% of ALI [24], or of 34% vs. 15% [11]. Oxygenation variables on admission or during the first 72 h have [21, 25, 26] or have not [23, 27, 28] been associated with outcome. Moreover, the moment from which oxygenation derangements start to have a prognostic value is uncertain. Villar et al. [15] analyzed the time issue with an interventional approach consisting in a PEEP trial of 5 cmH_2O. Those who persisted with PaO_2/FIO_2 of 150 or lower after 24 h had higher mortality and organ failures.

The findings of our study and those of Villar et al. [15] have in common the dynamic assessment of definitions. However, they used a fixed value of PEEP and a different PaO_2/FIO_2 cutoff point. Our higher PEEP level was set by the attending physician (mean PEEP at 24 h= 13 cmH_2O) in the conviction that different ARDS causes [29] and patients [30] require different PEEP levels. However, we found no differences in prognosis after 24 h except for a significant improvement in organ failure scores in the $ALI_{24\text{-h}}$ group. Low levels of selected PEEP, an insufficient number of patients, or differences in acuity could account for differences between the studies.

PaO_2/FIO_2 response to PEEP was similar in pulmonary and extrapulmonary ARDS. These results contradict the hypothesis of Gattinoni et al. [29] that ARDS-P and ARDS-EP behave as distinct entities in the initial stages of ARDS, with predominance of consolidation or of interstitial edema and alveolar collapse, respectively. Therefore differences between the two syndromes on CXR and computed tomography scan, in lung mechanics, and especially, in the response to PEEP and to recruitment maneuvers, are to be expected [31]. Van der Kloot et al. [32] have shown that recruitment maneuvers are less effective in an experimental ARDS model of pneumonia than in extrapulmonary ARDS models. In the clinical study of Lim et al. [33] patients with ARDS-EP had a greater increase in PaO_2 and a greater decrease in radiological scores after a recruitment maneuver. However, Puybasset et al. [34] found similar responses to PEEP-induced alveolar recruitment in ARDS-P and ARDS-EP patients, assessed by oxygenation and computed tomography. In respect to our results, we cannot discount that PEEP levels corresponding to ARDS-EP, theoretically the most "recruitable" group according to Gattinoni et al. [29], were insufficient. Similarly, response of PaO_2/FIO_2 to PEEP was indistinguishable in survivors and nonsurvivors.

The LIS remained stable in the overall cohort and in nearly all groups throughout the study, due to the opposite effects in total scoring produced by the increment of PEEP, vs. PEEP effects on oxygenation, CXR, and respiratory system compliance. After 24 h PaO_2/FIO_2 increased to more than 200 in 62% of patients ($ALI_{24\text{-h}}$ group) without changes in LIS. This suggests that the improvement in oxygenation was related to PEEP use and not to improvement in the underlying disease related to time. The only exception was in the $ARDS_{24\text{-h}}$ group, in which the increase in LIS could reflect a sicker patient or/a deteriorating condition. Indeed, this group showed less response to PEEP and a higher SOFA score.

The main disadvantage in the use of LIS is the lack of standardization of one of its components, the CXR [16, 17]. In our study investigators did not receive any special training for evaluating CXRs, as has been proposed, but this limitation is inherent to all. Nevertheless, assignment of scores for CXR between trained investigators and attending physicians seems to have an acceptable concordance [17].

The stability of the LIS in our study in most patients, in the face of an improved PaO_2/FIO_2 ratio after 24 h, questions previous statements about concordance and "interchangeability" between AECC definition and LIS [35]. Many investigators have observed that AECC definition and LIS score do not identify the same number of patients with ARDS in the same population [10, 11, 12] and specifically mention that these definitions cannot be indistinctly used [10]. This heterogeneity between studies may be due to differences in the severity of underlying illness or of the ARDS itself and, especially, to the intensity of therapeutic measures at the moment of diagnosis. A possible drawback of this study is the lack of a control group without PEEP. However, since PEEP is fundamental to the ventilatory management of ARDS, withholding it would be unadvisable in a clinical study.

In summary, this is one of the few studies attempting to quantify the effect of PEEP on ARDS definition. We found that the use of PEEP, as expected, improved PaO_2/FIO_2 so that most patients did not fulfill the oxygenation criteria of the AECC 24 h after ARDS diagnosis. Our data support the inclusion of PEEP level in the assessment of oxygenation for ALI/ARDS diagnosis. This could stratify acuity and contribute to homogenization of clinical studies.

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