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# Differences in the deflation limb of the pressure-volume curves in acute respiratory distress syndrome from pulmonary and extrapulmonary origin

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**Abstract** *Objective:* To assess the differences in the deflation pressure-volume (PV) curves between acute respiratory distress syndrome from pulmonary (ARDSp) and extrapulmonary (ARDSe) origin. *Design:* Prospective study. *Setting:* Twenty-bed intensive care unit in an university hospital. *Patients:* Ten patients within the first 24 h from meeting ARDS criteria, classified as ARDSp or ARDSe in a clinical basis. *Interventions:* A deflation PV curve was recorded by means of decreasing steps of continuous positive airway pressure (CPAP) from 35 to 0 $cmH_2O$. *Results:* The simultaneous recording of pressure at the airway opening (Pao), esophageal pressure (Pes) and volumes (V) allows us to trace the Pao-V, Pes-V and transpulmonary pressure (Ptp)-V curves. These data were fitted to a sigmoid model and ARDSp and ARDSe groups were compared. ARDSp has lower lung compliance and higher chest wall compliance than ARDSe (35.9±11.3 vs. 77.2±50.6 and 199.6±44.4 vs. 125.5±16.5 ml/$cmH_2O$, respectively, $P<0.05$). The Pao-V curve in ARDSp is shifted down and right with respect to ARDSe. The Ptp-V curve shows a similar displacement. The Pes-V curve in the ARDSp group is, however, shifted to the left. When relative values (percentage to the maximum volume achieved at 35 $cmH_2O$) are considered, these differences persist, but, in the Ptp-V curves, are only significant in the low-pressure range. *Conclusions:* Differences between ARDSp and ARDSe PV curves are present all along the pressure axis and are related to differences not only in the Pes-V curve, but also in the Ptp-V curve.

**Keywords** ALI/ARDS · Mechanical ventilation · Pressure-volume curves · Positive end-expiratory pressure · Continuous positive airway pressure.

## Introduction

One of the main differences between acute respiratory distress syndrome (ARDS) from pulmonary (ARDSp) and extrapulmonary (ARDSe) origin, as described originally by Gattinoni and colleagues [1] is the different recruitment capability. Namely, ARDSp has a poor response to positive end-expiratory pressure (PEEP) increments and sighs, whereas ARDSe shows a better response [1, 2].

For many years it has been proposed that PEEP should be titrated according to the presence of a lower inflection point on the inflation limb of the static pressure-volume (PV) curve of the respiratory system [3]. In fact, this could be related to a significant decrease in mortality [4]. However, other studies suggest that there is no rationale for this approach [5, 6, 7, 8] and that PEEP levels should be fixed according to the deflation limb of the PV curve, PEEP being an expiratory phenomenon. This setting could be beneficial in the context of an "open lung" approach to mechanical ventilation in ARDS [8].

However, there is very little known about the deflation limb of the PV curve in humans, nor about differences

between PV curves in ARDSp and ARDSe. The aim of this study is to compare deflation PV curves within these two groups of patients in the early phase of ARDS.

## Materials and methods

The protocol was approved by the Hospital Clinical Trials committee and informed consent was obtained from each patient's next of kin. Ten consecutive patients with ARDS diagnosis according to the published criteria [9] were included and assigned to ARDSp or ARDSe groups on a clinical basis (main diagnosis, radiological and microbiological data, including samples from the respiratory tract in all patients, and surgical findings) before any measurement. Age, sex, height and weight, main diagnosis and cause of ARDS, $PaO_2$ to $FiO_2$ ratio, APACHE II severity index [10] and lung injury score [11] were registered for each patient. All patients were studied within the first 24 h of fulfilling ARDS criteria. Exclusion criteria were chronic lung disease, air leaks through chest tubes, previous chest wall abnormalities and any other contraindication for increasing airway pressure (i.e., brain trauma or severe hemodynamic inestability).

Patients were intubated and ventilated with an Evita 4 ventilator (Dräger, Lubeck, Germany) in a semirecumbent position. All of them were receiving intravenous benzodiazepines, opioids and non-depolarizing neuromuscular blocking agents during the procedure for a Ramsay score of 5 and complete absence of respiratory efforts. The patient's electrocardiogram, heart rate, blood pressure and $SpO_2$ were continuously measured.

Esophageal pressure was recorded with a fluid-filled catheter (Salem stomach tube no. 16, Argyle, Sherwood Medical Ltd., Belgium), according to the previously published technique [12]. Validation of catheter position was done in relaxed patients by means of a thoracic compression during an end-inspiratory pause [13, 14]: an increment ratio of 1:1 in esophageal and airway pressures was considered as a marker of correct catheter positioning. The catheter was connected to a pressure transducer (Transpac monitoring kit, Abott, Sligo, Ireland) and derived to a bedside monitor. Esophageal pressure tracing was plotted against time and data collected in a laptop computer.

Airway pressure and delivered volumes were measured using the built-in pressure transducer and pneumotachograph of the ventilator. Values are given at body temperature and pressure saturated (BTPS conditions). Accuracy of the data was proven by comparing pressures with a pressure transducer connected through a side port at the endotracheal tube opening and by measuring volumes with a 1-l calibration syringe previously to the experiment (data not shown). The data were also transferred to the laptop computer from the ventilator using the EvitaView software (Dräger, Lubeck, Germany).

Once the patient was monitored, the cuff of the endotracheal tube was inflated with an extra volume of 2–3 ml of air, and the airway was suctioned free of secretions. All equipment connections were revised to avoid air leaks, which were detected during an end-inspiratory pause by observing no changes in airway pressure. Then, the deflation PV-curve maneuver was performed (Fig. 1). After standardization of volume history with three large breaths (tidal volume >12 ml/kg), the ventilator was switched to continuous positive airway pressure (CPAP) mode at zero pressure level, allowing the lungs to deflate. When flow was zero, the pressure level was raised to 35 $cmH_2O$ until reaching a new equilibrium. The insufflated volume at this airway pressure was recorded (Vmax). The pressure level was then decreased in 5-$cmH_2O$ steps until 0 $cmH_2O$. The exhaled volume and the esophageal pressure at each step were also recorded. With these data, three PV curves were traced: airway opening pressure-volume (Pao-V) curve, esophageal pressure-volume (Pes-V) curve and transpulmonary pressure-volume (Ptp-V) curve. Ptp was calculated as Pao minus Pes. This method for PV curve constructing has shown an excellent correlation with the supersyringe technique in benchmark and animal studies (intraclass correlation coefficients higher than 0.85 for each pressure level, $P<0.05$, unpublished data).

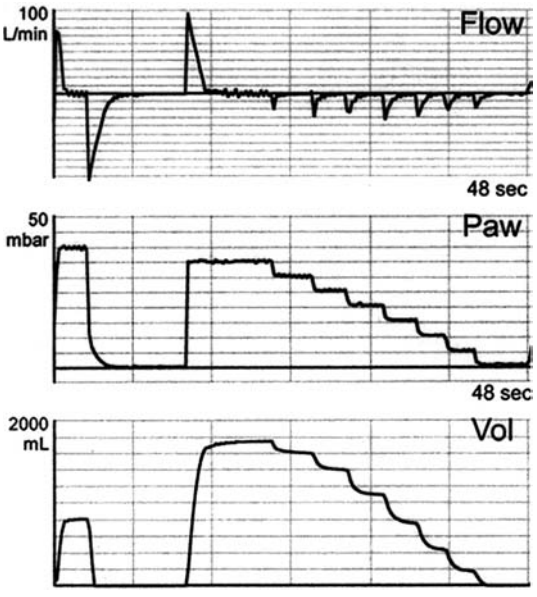


**Fig. 1** Maneuver for pressure-volume curve constructing. After a prolonged expiration, airway pressure is set to 35 $cmH_2O$ until a new steady state is reached. Then the pressure is decreased in 5-$cmH_2O$ steps until 0 $cmH_2O$. The EvitaView software samples airway pressure (*Paw*), volume (*Vol*) and flow at a rate of 125 Hz. Simultaneously to these measurements, esophageal pressure is recorded

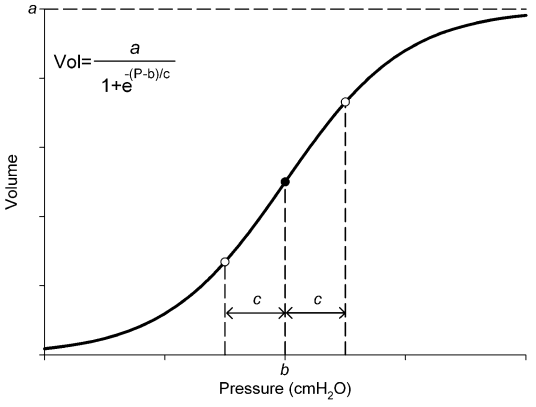


**Fig. 2** Schematic representation of the mathematical model with its equation. Volume is calculated from pressure using three fitting parameters (*a*, *b*, *c*). The meaning of these parameters is explained in the text (materials and methods and discussion sections). Modified from [6] with permission

Compliances were measured over the curves as chord compliance (the slope of the straight line between 0 and the maximal volume/pressure obtained).

The curves were fitted to a sigmoid model modified from that previously published by Venegas et al. [15]. In this model, volume is expressed as a function of total lung capacity (*a*), the mathematical inflection point of the curve (where curvature changes sign) (*b*), a parameter related to the pressure range around the mathe-

**Table 1** Patients' characteristics: diagnosis, age and sex, APACHE-II score (*A-II*), lung injury score (*LIS*), height, weight and predicted body weight (*PBW*), ARDS origin and outcome (*S* survivor. *D* dead). *BMT* bone marrow transplant, *AIDS* acquired immunodeficiency syndrome

| No. | Diagnosis | Cause of ARDS | Age | Sex | A-II | $PaO_2/FiO_2$ | LIS | Weight | Height | PBW | Origin | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Autologous BMT | Pneumonia | 55 | M | 18 | 187 | 2.5 | 68 | 1.74 | 69.7 | ARDSp | D |
| 2 | Pneumonia | Pneumonia | 80 | F | 27 | 122 | 2.5 | 68 | 1.57 | 49.7 | ARDSp | S |
| 3 | Fournier gangrene | Septic shock | 81 | M | 23 | 140 | 3.25 | 70 | 1.63 | 59.6 | ARDSe | D |
| 4 | Peritonitis | Septic shock | 58 | M | 23 | 96 | 3.25 | 57 | 1.65 | 61.5 | ARDSe | S |
| 5 | Pneumonia | Pneumonia | 58 | M | 18 | 57 | 2.75 | 65 | 1.72 | 67.8 | ARDSp | D |
| 6 | Leptospirosis | Alveolar hemorrhage | 46 | M | 31 | 168 | 3 | 67 | 1.65 | 61.5 | ARDSp | S |
| 7 | Perforated ulcer | Hemorrhagic shock | 42 | F | 19 | 163 | 2.75 | 42 | 1.47 | 40.6 | ARDSe | D |
| 8 | AIDS | Pneumonia | 35 | M | 34 | 30 | 3.25 | 60 | 1.74 | 69.7 | ARDSp | S |
| 9 | Bowel perforation | Septic shock | 70 | M | 24 | 118 | 2.75 | 70 | 1.62 | 58.7 | ARDSe | S |
| 10 | Pancreatitis | Septic shock | 67 | M | 11 | 160 | 3 | 65 | 1.53 | 50.5 | ARDSe | S |
| Mean | | | 59.2 | | 22.8 | 124 | 2.9 | 63.2 | 1.6 | 58.9 | | |
| SD | | | 15.5 | | 6.76 | 50 | 0.3 | 8.5 | 0.1 | 9.5 | | |

matical inflection point in which most change of volume takes place (*c*) and airway pressure (P). This model is represented in Fig. 2. This fitting allows us to calculate in Pes-V and Ptp-V curve volumes corresponding to the same pressure levels for comparing ARDSp and ARDSe groups (volumes corresponding to Pes of 16 to 0 $cmH_2O$ in 2-$cmH_2O$ steps and volumes corresponding to Ptp of 25 to 0 $cmH_2O$ in 5-$cmH_2O$ steps were calculated using the equation). These maximum pressure levels were selected in order to avoid extrapolation of data outside of the ranges studied. Comparisons were done using the absolute values of volume, expressed as milliliters per kilogram of predicted body weight (PBW), and the fractional volume to maximum volume achieved. This was done to avoid the individual variability of lung capacity, which is related not only to each patient's characteristics (age, sex, height and weight), but also to ARDS severity itself.

For statistical analysis, all data are expressed as mean ± standard deviation. Fitting to the model was performed by regression analysis using the least squares method. Lung volumes in ARDSp and ARDSe groups were compared for the same pressure levels using the Mann-Whitney U test, as well as demographic and clinical data. A *P* value equal to 0.05 or smaller was considered statistically significant.

## Results

### Patients

Ten patients were studied (Table 1). Mean age was 59.9±15.5 years. The mean APACHE-II score and lung injury score were 22.8±6.8 and 2.9±0.3, respectively. There were not any incidents during the maneuver, which took less than 40 s in all cases. No differences were found between ARDSp and ARDSe groups in these data (Table 2). Maximum transpulmonary pressures were 29.65±1.00 and 22.5±3.84 cmH2O for ARDSp and ARDSe groups ($P<0.05$ for the difference).

### Compliances

Both groups show similar respiratory system compliance (ARDSe: 45.3±18.1 ml/$cmH_2O$; ARDSp: 30.3±8.8 ml/

**Table 2** Patients' characteristics in ARDSp and ARDSe groups

| | ARDSp | ARDSe | *P* |
|---|---|---|---|
| Age | 54.8±16.7 | 63.6±14.6 | 0.30 |
| Height (cm) | 168±7 | 158±8 | 0.06 |
| Weight (kg) | 65.6±3.4 | 60.8±11.8 | 0.84 |
| Predicted body weight (kg) | 63.7±8.5 | 54.2±8.7 | 0.10 |
| APACHE-II | 25.6±7.4 | 20.0±5.4 | 0.34 |
| $PaO_2/FiO_2$ | 112.7±68.2 | 135.4±28.5 | 0.92 |
| Lung injury score (LIS) | 2.8±0.33 | 3.0±0.25 | 0.28 |
| Respiratory system compliance (Crs) | 30.0±8.7 | 45.0±18.1 | 0.08 |
| Lung compliance (CL) | 35.9±11.3 | 77.2±50.6 | 0.04 |
| Chest wall compliance (Cw) | 199.6±44.4 | 125.5±16.5 | 0.02 |

**Table 3** Curve fitting parameters in ARDSp and ARDSe groups. Their physiological correlates are: *a* total lung capacity; *b* mathematical inflection point; *c* range of pressures around *b* where most change of volume occurs. See text for further details

| Parameters | ARDSp | ARDSe | *P* |
|---|---|---|---|
| Pao-V curve | | | |
| *a* (ml/kg PBW) | 17.37±4.65 | 31.09±11.02 | 0.04 |
| *b* ($cmH_2O$) | 18.01±2.53 | 14.31±2.39 | 0.04 |
| *c* ($cmH_2O$) | 5.39±1.43 | 6.85±1.58 | 0.12 |
| Ptp-V curve | | | |
| *a* (ml/kg PBW) | 17.4±4.7 | 32.75±12.4 | 0.04 |
| *b* ($cmH_2O$) | 15.45±2.70 | 10.00±3.36 | 0.03 |
| *c* ($cmH_2O$) | 4.37±1.20 | 4.78±2.16 | 0.92 |
| Pes-V curve | | | |
| *a* (ml/kg PBW) | 18.64±4.3 | 31.14±8.91 | 0.03 |
| *b* ($cmH_2O$) | 2.59±0.33 | 5.04±2.40 | 0.14 |
| *c* ($cmH_2O$) | 0.97±0.31 | 2.26±0.75 | 0.01 |

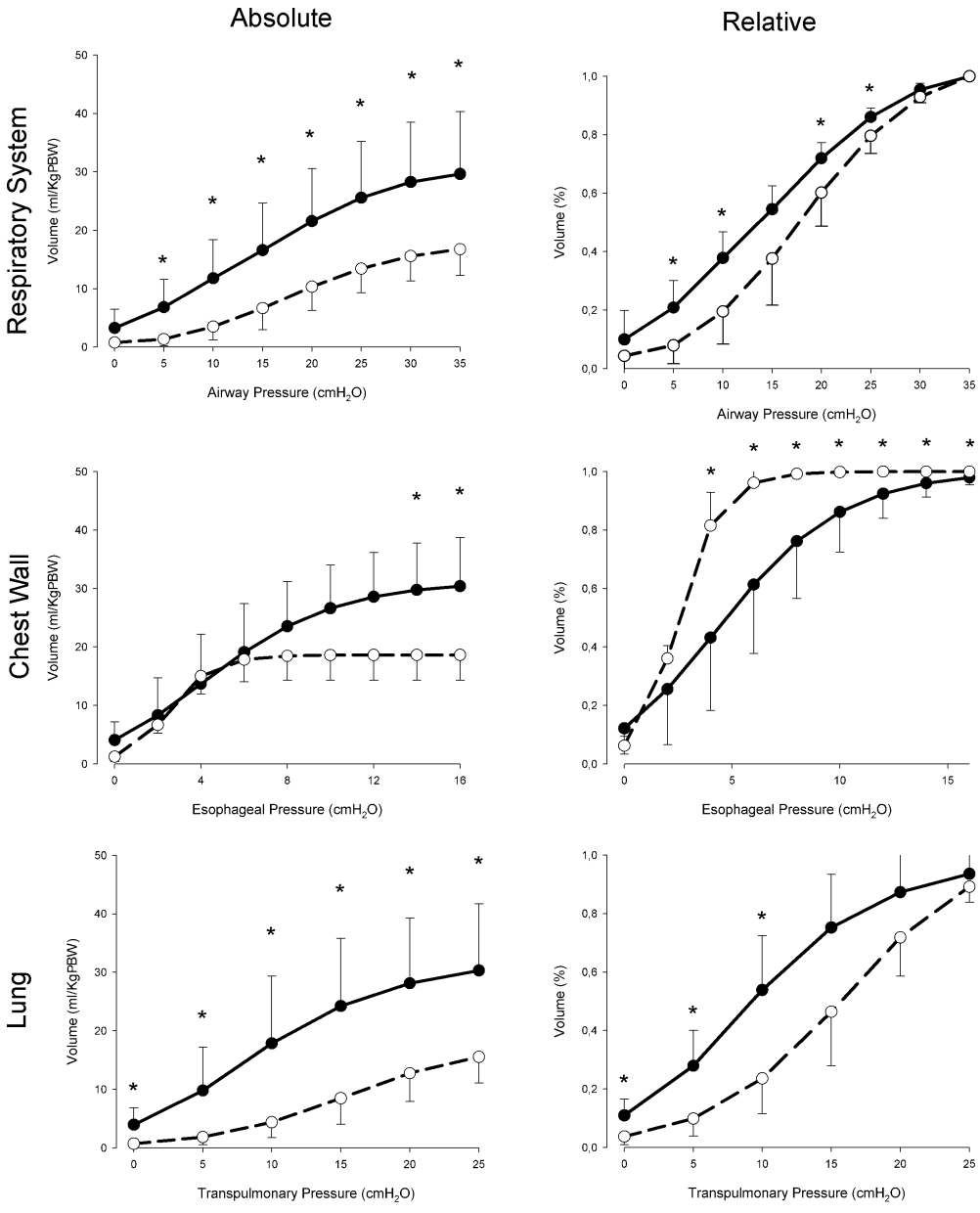


**Fig. 3** Pressure-volume curves: Upper row: Airway pressure-volume curves; Middle row: Esophageal pressure-volume curves; Lower row: Transpulmonary pressure-volume curves. Left: Absolute volume values. Right: volumes (as a fraction of Vmax). *p<0.05 for the difference between ARDS from pulmonary (dotted line) and extrapulmonary (continous line) origin.

$cmH_2O$, $P$=0.08), but ARDSe has a higher lung compliance (77.28±50.6 ml/$cmH_2O$ vs. 35.9±11.3 ml/$cmH_2O$, $P$<0.05) and lower chest wall compliance (125.5± 16.5 ml/$cmH_2O$ vs. 199.6±44.4 ml/$cmH_2O$, $P$<0.05).

## Fitting

The fitting of the data to the sigmoid model was excellent, being mean $R^2$ 0.99±0.02 for the Pao-V curve, 0.99±0.006 for the Pes-V curve and 0.99±0.005 for the Ptp-V curve.

The fitting parameters are shown in Table 3. There is a good correlation between Vmax and the estimated parameter $a$ in the Pao-V curve ($r$=0.966, $P$<0.001, slope =0.91, y-intercept =34 ml), the Pes-V curve ($r$=0.956, $P$<0.01, slope =1, y-intercept =–93 ml) and the Ptp-V curve ($r$=0.967, $P$<0.001, slope =0.91, y-intercept =43 ml). The ARDSe group has a trend towards a higher Vmax (31.09±11.03 ml/kgPBW vs. 17.37±4.65 ml/kgPBW, $P$=0.08). In the fitting parameters, this group has a higher estimated lung capacity ($a$) in the three curves. The mathematical inflection point ($b$) is placed at higher pressures in the ARDSp group in the Pao-V and Ptp-V curves. On the other side, the only difference between groups in the Pes-V curve fitting is the pressure range around $b$ in which most of the change of volume occurs ($c$).

PV curves (Fig. 3)

The Pao-V curve in the ARDSp group shows a displacement down and right along all the pressure axis, with significant differences in volumes at pressures from 5 to 35 $cmH_2O$. If fractional volumes are considered, these differences remain, but they are small in magnitude.

When considering Ptp-V curves, the shift of the curve in the ARDSp group occurs in a similar way, but difference in volume is statistically significant in all calculated pressures. In the Ptp-fractional volume curve, these differences are only significant in the low-pressure range (this is at 0, 5 and 10 $cmH_2O$) (Fig. 3).

There are no differences in the Pes-V curves in the pressure range between 0 and 14 $cmH_2O$. From this point on, the curve in the ARDSe group has a trend to higher volumes. In an opposite way, the Pes-fractional volume curve in the ARDSe group is shifted to the right, being lower in volume than in the ARDSp group in the pressure range between 4 and 16 $cmH_2O$.

## Discussion

The use of PEEP as a treatment for hypoxemia in ARDS patients has been the mainstay of the ventilatory management of this disease since its description [16]. However, criteria used for PEEP setting have been quite variable during this time, and very different approaches have been used, from a fixed combination of $FiO_2$ and PEEP [17] to more physiologic approaches, based on measurements of static lung mechanics or hemodynamics. The most extended of these concepts uses the inspiratory limb of the PV curve and the definition of an "inflection point" (which is really a point of maximum curvature), above which PEEP must be set [3]. In fact, the use of these measurements on PV curves for mechanical ventilation setting could be associated with a decrease in mortality in ARDS patients [4]. The physiologic rationale underlying this is that the tidal cycle is moved to the steeper part of the inspiratory PV curve. However, there is increasing evidence that challenges this approach, from theoretic [5, 6], experimental [7, 18] and clinical grounds [19]. PEEP is an expiratory phenomenon that avoids alveolar collapse, but the amount of aerated tissue depends on the tidal recruitment obtained [7, 19]. It seems more reasonable to use the deflation limb of the PV curve for PEEP setting, as proposed first by Holzapfel [20] and later by other authors [8, 18, 21].

The deflation limb of the PV curve has been less studied than the inflation one, maybe due to methodological concerns about the accuracy of measurements made with the super-syringe method [22, 23]. Moreover, other techniques for tracing PV curves, as the low-flow technique or the inspiratory occlusions technique, don't allow the obtaining of static measurements of the deflation limb of the PV curve. Our method provides a simple way for obtaining this deflation limb, without disconnecting the patient from the ventilator and with little additional equipment. In a rat model, this method has shown an excellent correlation with the super-syringe technique before and after lung injury (being bias and precision of the method 0.32±0.78 ml, unpublished data). The short time used in the maneuver makes the results less prone to errors resulting from oxygen uptake (which is the main cause of error in the expiratory measurements). Other sources of error when tracing PV curves in ARDS patients ventilated with high $FiO_2$s is the presence of lung collapse due to absortion atelectasis [24]. However, the large breaths previous to the maneuver and the CPAP level used in these patients (starting from 35 cmH2O and allowing the respiratory system to reach an equilibrium) can recruit these atelectatic zones [24].

Our results agree with those from Gattinoni et al. [1] in the differences in lung and chest wall compliances between ARDSp and ARDSe. There is a trend towards higher respiratory system compliance in the ARDSe group, which could be related to the higher severity of the ARDSp group patients (higher APACHE-II score and lower $PaO_2/FiO_2$ ratio, although without statistical significance). These results might be influenced by the fact that maximum pressure reached during the study protocol was 35 $cmH_2O$. This pressure level is surely related to an incomplete recruitment of the lungs, but the volumes delivered to the patients were above 1 l in almost all the cases. The limit at 35 $cmH_2O$ was fixed according to the recommendations of the consensus conference [26], so that our results were applicable to the therapeutic pressure range.

Moreover, our data reflect that differences between ARDSp and ARDSe are extended not only to a shift of the respiratory system PV curve to the right due to the decreased chest wall compliance in the ARDSe group, but also to a different lung volume for the same transpulmonary pressure and, in consequence, to different mechanical properties of the lung tissue itself. It seems reasonable to hypothesize that in ARDSp the alveolar consolidation results in a very small lung capacity, because of the lack of recruitment during the inspiratory phase [19]. In contrast, the lung in ARDSe has a major injury in the interstitium, with relatively preserved alveolar spaces, which results in the observed higher volumes. The persistence of these differences along the whole of the pressure range during expiration could explain the higher response to PEEP in the ARDSe group, because of a higher non-derecruited volume at the same PEEP level.

The comparison of fractional volumes in the Ptp-V curve shows that the differences are limited to the low-pressure range. The finding of higher fractional volumes at low pressures suggests a participation of airway closure in the ARDSe, which promotes air trapping in the

lung. This assumption is derived from the fact that pressures required for recruitment of atelectatic lung tissue are very high, in contrast to the opening and closure of small airways that happen at lower pressures [27]. This hypothesis has also been suggested when comparing inflation PV curves among healthy men under anesthesia in ZEEP and PEEP conditions [28]. The inflection point in the deflation limb (*b*) has been related to the beginning of airway closure [29].

Taken together, our results suggest that PEEP required to avoid lung collapse and airway closure is higher in the ARDS from pulmonary origin (around 4–5 $cmH_2O$ in the studied patients, see Table 3), in spite of a smaller amount of recruitable lung tissue. Our experimental design does not allow us to directly demonstrate differences in closing volume, pressure or functional residual capacity, so more studies are warranted.

We add the measurements of esophageal pressures because of the concerns of the role of the chest wall in respiratory mechanics in ARDS. The use of esophageal pressure in semirecumbent patients is a matter of debate, but it has been proved that increases in Pes have a very good correlation with increases in pleural pressure [7, 25]. Differences in the Pes-V curves lie on parameters *a* and *c*. Differences in *a* are related to the fact that the elastic limit of the curves is determined primarily by the lung tissue. Differences in *c* reflect a different behavior of the chest wall (volume decrease is quite abrupt in the ARDSp and occurs in a slower way in the ARDSe). Thus, the range of PEEP levels that counteract the influence of the chest wall should be narrower in the ARDSp than in the ARDSe.

In 1997, two papers from Ranieri and colleagues [30] and Mergoni and colleagues [31] related the abnormalities in chest wall PV curve with the presence of inflection points in the inflation limb of the PV curve of the respiratory system, its shape and the response to PEEP. Our results agree with these previous works in the shift of the Pes-V curve to the right in the ARDSe group. However, we do not find the displacement of the Ptp-V curve to the right seen in the work from Ranieri [30], but to the left. The fact that we use different techniques, the study of the deflation instead of the inflation limb of the PV curve and the different criteria for classifying patients (medical and surgical versus pulmonary and extrapulmonary, some medical ARDS being from extrapulmonary origin) might have caused these differences. In spite of these disappointments, our results reinforce the evidence presented in these previous articles about the large impact of the chest wall mechanics in ARDS. However, the practical value of esophageal pressure measurements on the critical care arena remains to be determined.

In conclusion, our findings suggest that: (1) differences between ARDSp and ARDSe are not limited to the lineal respiratory system compliance, but they extend along the whole deflation pressure range; (2) the chest wall has a great impact in respiratory system mechanics in ARDS, with different volumes at the same pressures and a different deflation kinetics in ARDSp and ARDSe; (3) moreover, lung mechanics are also different, with a higher lung volume at any transpulmonary pressure in the ARDSe group. A different approach to PEEP setting based on ARDS origin should be evaluated in a prospective manner.

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