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Alveolar Recruitment in Pulmonary and Extrapulmonary Acute Respiratory Distress Syndrome

Comparison Using Pressure–Volume Curve or Static Compliance

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Background: **Alveolar recruitment in response to positive end-expiratory pressure (PEEP) may differ between pulmonary and extrapulmonary acute respiratory distress syndrome (ARDS), and alveolar recruitment values may differ when measured by pressure–volume curve compared with static compliance.**

Methods: **The authors compared PEEP-induced alveolar recruitment in 71 consecutive patients identified in a database. Patients were classified as having pulmonary, extrapulmonary, or mixed/uncertain ARDS. Pressure–volume curves with and without PEEP were available for all patients, and pressure–volume curves with two PEEP levels were available for 44 patients. Static compliance was calculated as tidal volume divided by pressure change for tidal volumes of 400 and 700 ml. Recruited volume was measured at an elastic pressure of 15 cm H_2O.**

Results: **Volume recruited by PEEP (10 ± 3 cm H_2O) was 223 ± 111 ml in the pulmonary ARDS group (29 patients), 206 ± 164 ml in the extrapulmonary group (16 patients), and 242 ± 176 ml in the mixed/uncertain group (26 patients) ($P = 0.75$). At high PEEP (14 ± 2 cmH_2O, 44 patients), recruited volumes were also similar ($P = 0.60$). With static compliance, recruitment was markedly underestimated and was dependent on tidal volume (226 ± 148 ml using pressure–volume curve, 95 ± 185 ml for a tidal volume of 400 ml, and 23 ± 169 ml for 700 ml; $P < 0.001$).**

Conclusion: **In a large sample of patients, classification of ARDS was uncertain in more than one third of patients, and alveolar recruitment was similar in pulmonary and extrapulmonary ARDS. PEEP levels should not be determined based on cause of ARDS.**

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ACUTE respiratory distress syndrome (ARDS) is characterized by severe hypoxemia, bilateral infiltrates, reduced respiratory system compliance, and reduced functional residual capacity.[1] Positive end-expiratory pressure (PEEP) is the standard of care for recruiting collapsed alveoli.[2] The efficacy of PEEP in improving functional residual capacity and gas exchange depends on respiratory mechanics,[3,4] ventilator settings,[5,6] and disease stage.[7,8] Recently, Gattinoni *et al.*[9] reported evidence that the efficacy of PEEP in recruiting collapsed alveoli differed according to the cause of ARDS, being far less in patients with primary pulmonary disease, such as pneumonia or aspiration, than in patients with extrapulmonary disease, such as abdominal sepsis.[9] The volume recruited by PEEP is usually assessed based on the static pressure–volume (P-V) curve of the respiratory system. Alveolar recruitment leads to an upward shift along the volume axis of the P-V curve with PEEP, compared with the curve with zero end-expiratory pressure, and is quantified as the volume increase with PEEP at the same elastic pressure.[3,6,10–12] Gattinoni *et al.* replaced the P-V curves with PEEP and without PEEP by the linear P-V relation from end-expiration to end-inspiration. However, this method may underestimate or overestimate alveolar recruitment with PEEP, because of the nonlinear behavior of the static P-V relation of the respiratory system. In addition, the population studied by Gattinoni *et al.*[9] may not be representative of the heterogeneous population of patients with ARDS seen in clinical practice. An effect of the underlying disease on the efficacy of PEEP in recruiting collapsed alveoli might have implications for the treatment of ARDS. To look for evidence supporting such an effect, we examined a large international database of patients with ARDS due to pulmonary or extrapulmonary disease.

Materials and Methods

Patients

In the database, we found 71 patients who received mechanical ventilation for ARDS and for whom P-V curves were available. The patients came from different studies and from three different teaching hospitals, 35 from the Henri Mondor Teaching Hospital, Creteil, France[3,6]; 18 from the Charles Nicolle Teaching Hospital, Rouen, France[13]; and 18 from the Policlinico Teach-

Table 1. Characteristics of the Patients (n = 71)

Demographic and Clinical Characteristics	Mean ± SD [Median]
Age, yr	51 ± 17 [48]
Male, n (%)	43 (61)
SAPS II	47 ± 21 [44]
Intensive care unit mortality, n (%)	37 (52)
Duration of ARDS, days	4 ± 3 [3]
Origin of ARDS, No. of patients (%)	
Pulmonary ARDS	29 (41)
Extrapulmonary ARDS	16 (22)
ARDS of mixed or uncertain cause	26 (37)

ARDS = acute respiratory distress syndrome; SAPS = Simplified Acute Physiology Score.

ing Hospital, Bari, Italy.[4,14] All the studies were approved by each institutional ethics committee, and written consent was obtained before each inclusion. ARDS was defined using the criteria developed by the American-European Consensus Conference on ARDS.[1] Patient characteristics are reported in table 1.

Classification of ARDS

Three senior intensivists who had extensive experience with mechanical ventilation and ARDS used information from the hospital records to classify the patients as having pulmonary ARDS, extrapulmonary ARDS, or ARDS of mixed or uncertain origin. They were not otherwise involved in the study, worked independently of one another, and were unaware of the P-V curve results. Pulmonary ARDS was defined as ARDS due to pneumonia, aspiration, inhalation injury, alveolar hemorrhage, or pulmonary contusion; and extrapulmonary ARDS was defined as ARDS due to sepsis-related to abdominal or extraabdominal infection, acute pancreatitis, trauma, cardiopulmonary bypass, or massive blood transfusion. Each expert indicated whether the classification was definite, probable, or doubtful. Patients were classified as having pulmonary ARDS when all three experts agreed on definite or probable pulmonary ARDS, or when two agreed and the third selected ARDS of mixed or uncertain origin. Classification in the extrapulmonary ARDS category was done in the same way, substituting extrapulmonary for pulmonary. Patients who met neither the criteria for pulmonary ARDS nor those for extrapulmonary ARDS were classified as having ARDS of mixed or uncertain origin.

Pressure–Volume Curves

All of the study patients were ventilated with a Siemens Servo 900C ventilator (Siemens Elema AB, Berlin, Germany) and underwent P-V curve recording with and without PEEP to assess respiratory mechanics and recruitment of previously collapsed alveoli. All P-V curves were performed after a 6-s pause to eliminate intrinsic PEEP. P-V curves were recorded using the low-flow method at two centers (53 patients) and the multiple-

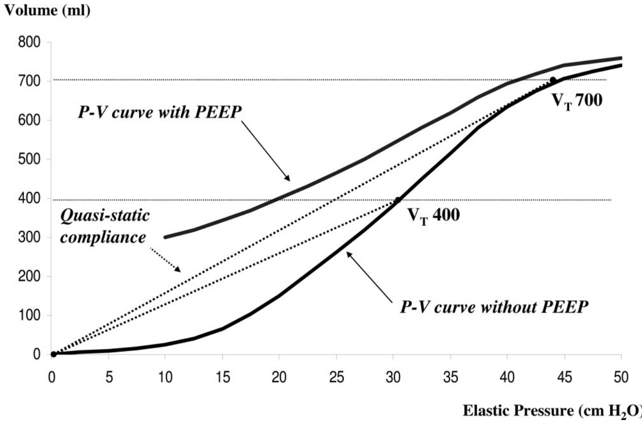

Fig. 1. Quasi–static compliance was calculated from the pressure–volume (P-V) curve as the tidal volume divided by the change in elastic pressure, with tidal volumes of 400 ml (V_T400) and 700 ml (V_T700). PEEP = positive end-expiratory pressure.

occlusion method at one center (18 patients). The low-flow method using a computer-controlled Servo Ventilator 900C has been described in detail elsewhere.[15] The multiple-occlusion method involved a series of breath tests at different inflation volumes, as previously described.[10] With both methods, the volume recruited by PEEP was defined as the difference between the volume measured on the curve starting from PEEP and the volume measured on the curve starting from zero end-expiratory pressure at a static pressure of 15 cm H_2O. To identify the upward shift along the volume axis of the P-V curve with PEEP relative to the P-V curve without PEEP, the P-V curve from PEEP was plotted on the same volume axis using the volume variation during passive expiration from PEEP to zero end-expiratory pressure (fig. 1). This volume represents the variation in end-expiratory lung volume induced by PEEP. In 44 patients, two sets of P-V curves were obtained, with high and low PEEPs, respectively.

Compliance and Calculation of Alveolar Recruitment

Because Gattinoni *et al.*[9] used the static compliance method, we also compared this method with the P-V curve method. Static compliance is usually calculated as tidal volume divided by the variation of elastic pressure between end-inspiration and end-expiration. An occlusion maneuver is performed to measure the elastic pressure only, eliminating resistive pressure because of a zero flow. We calculated quasi–static compliance (C_{qST}) from the P-V curve (which give the quasi–static pressure value for any inflated volume with a low flow) by tracing a straight line between zero and the two P-V points on the curve corresponding to tidal volumes of 700 ml (V_T700) and 400 ml (V_T400) from zero end-expiratory pressure. Each P-V curve started after a 6-s expiration to eliminate intrinsic PEEP. Recruitment evaluated using C_{qST} was calculated as the difference in volume between

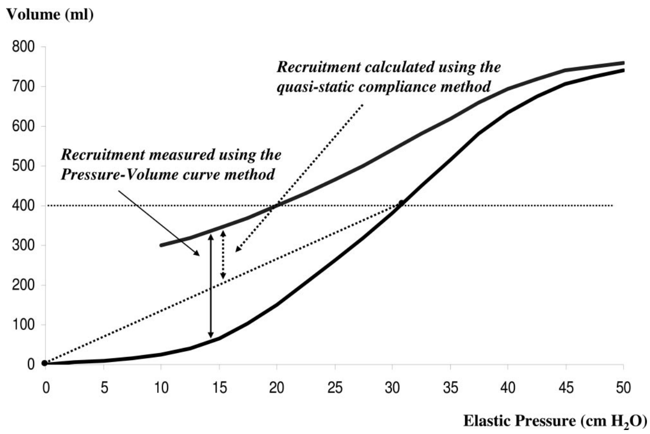

Fig. 2. Comparison of the pressure–volume curve method and the quasi–static compliance method for calculating alveolar recruitment. The upward shift of the pressure–volume curve with positive end-expiratory pressure indicates alveolar recruitment induced by positive end-expiratory pressure. Quasi–static compliance may be unreliable for assessing the effect of positive end-expiratory pressure on recruitment, because it does not take into account the sinusoidal shape of the pressure–volume curve, which reflects the behavior of the respiratory system.

the P-V curve with PEEP and the slope of C_{qST} at 15 cm H_2O elastic pressure, as shown in figure 2.

Statistical Analysis

All data are expressed as mean ± SD [median]. Alveolar recruitment values determined using the P-V curve method and using the C_{qST} method at V_T400 and V_T700 were compared using one-way analysis of variance. Alveolar recruitment and clinical characteristics in the pulmonary, extrapulmonary, and mixed or uncertain groups were also compared by analysis of variance. When analysis of variance was significant, a Bonferroni *post hoc* test was performed to determine differences between individual means. *P* values of 0.05 or less were considered statistically significant. The SPSS package was used for all statistical tests (SPSS Inc., Chicago, IL).

Results

Of the 71 patients, 29 (41%) were classified in the pulmonary ARDS group, 16 (22%) were classified in the extrapulmonary ARDS group, and 26 (37%) were classified in the mixed/uncertain origin group. Table 2 reports the main differences across the three groups. C_{qST} was similar in the three groups. Patients with ARDS of mixed/uncertain origin were older and more seriously ill than patients in the other two groups, although mortality was similar. Of the 44 patients who had two sets of P-V curves (two PEEP levels), 21 (47%) were in the pulmonary ARDS group, 6 (14%) were in the extrapulmonary ARDS group, and 17 were (39%) in the mixed/uncertain origin group. Mean PEEP was 10.5 ± 2.9 cm H_2O overall (n = 71) and 14.2 ± 1.7 cm H_2O in the 44 patients who had P-V curves at a higher PEEP level.

Alveolar Recruitment Evaluated Using P-V Curves in the Three Groups

The P-V curves at a PEEP level of 10.5 ± 2.9 cm H_2O showed no differences in alveolar recruitment across the three groups: 223 ± 111 ml in the pulmonary ARDS group, 206 ± 164 ml in the extrapulmonary ARDS group, and 242 ± 176 ml in the mixed/uncertain origin group ($P = 0.75$). No significant differences were found when curves at a higher PEEP level were used to evaluate alveolar recruitment (44 patients): 446 ± 180 ml in the pulmonary ARDS group, 377 ± 242 ml in the extrapulmonary ARDS group, and 396 ± 165 ml in the mixed/uncertain origin group ($P = 0.60$; fig. 3).

Comparison of the P-V Curve Method and Quasi–Static Compliance Method

In the overall population, alveolar recruitment was 226 ± 148 ml by the P-V curve method, 95 ± 185 ml by the C_{qST} method with V_T400, and 23 ± 169 ml by the C_{qST} method with V_T700 ($P < 0.01$). In the 44 patients who

Table 2. Comparison between Patients with Pulmonary ARDS and Those with Extrapulmonary ARDS

	Pulmonary ARDS (n = 29)	Extrapulmonary ARDS (n = 16)	ARDS of Mixed or Uncertain Cause (n = 26)	*P* Value
Age, yr	47 ± 16	46 ± 17	60 ± 14†	0.003
SAPS II	44 ± 18	38 ± 19	55 ± 22*	0.02
Intensive care unit mortality, n (%)	13 (45)	9 (56)	15 (58)	0.59
Duration of ARDS, days	4 ± 3	4 ± 3	5 ± 4	0.29
C_{qST}, ml/cm H_2O				
C_{qST} V_T400 ml	36 ± 14	29 ± 13	38 ± 20	0.21
C_{qST} V_T700 ml	41 ± 14	34 ± 13	42 ± 19	0.30
PEEP level, cm H_2O				
Low PEEP (n = 71)	10.1 ± 2.5	11.8 ± 2.6	10.3 ± 3.3	0.13
High PEEP (n = 44)	14.1 ± 1.9	14.0 ± 1.5	14.4 ± 1.5	0.88

Values were compared by analysis of variance.

* $P \leq 0.05$ between mixed or uncertain *versus* extrapulmonary acute respiratory distress syndrome (ARDS). † $P \leq 0.05$ between mixed or uncertain *versus* extrapulmonary and pulmonary ARDS.

C_{qST} = quasi–static compliance of the respiratory system; PEEP = positive end-expiratory pressure; SAPS = Simplified Acute Physiology Score; V_T = tidal volume.

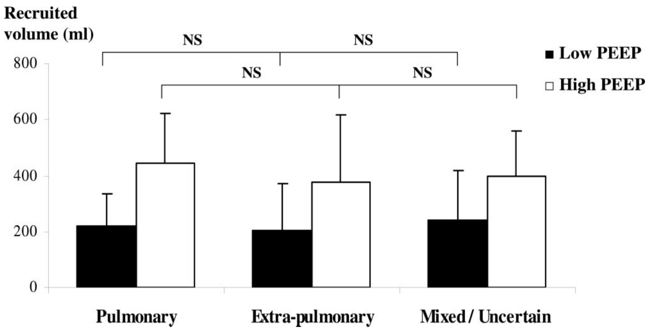

Fig. 3. Comparison of positive end-expiratory pressure (PEEP) recruitment evaluated using the pressure–volume curve in patients with pulmonary acute respiratory distress syndrome, extrapulmonary acute respiratory distress syndrome, or acute respiratory distress syndrome of mixed or uncertain origin. PEEP-induced recruitment was similar in the three groups, P = 0.60 with a high PEEP level (*white squares*) and P = 0.75 with a lower PEEP level (*black squares*), by analysis of variance. NS = not significant.

had P-V curves at a higher PEEP level, alveolar recruitment was 417 ± 181 ml by the P-V curve method, 225 ± 187 ml by the C_{qST} method with V_T400, and 144 ± 159 ml by the C_{qST} method with V_T700 ($P < 0.01$; fig. 4).

Discussion

In our large sample of patients, PEEP-induced alveolar recruitment was not influenced by the cause of ARDS, whatever the PEEP level. There was the same potential for alveolar recruitment in patients with pulmonary ARDS and in those with extrapulmonary ARDS. In addition, the C_{qST} method resulted in marked underestimation of alveolar recruitment compared with the P-V curve method. These results are consistent with findings from other studies.[16,17] They suggest that the PEEP level should not be selected based on the cause of ARDS. In addition, we found that approximately one third of patients could not be readily classified as having pulmonary or extrapulmonary ARDS.

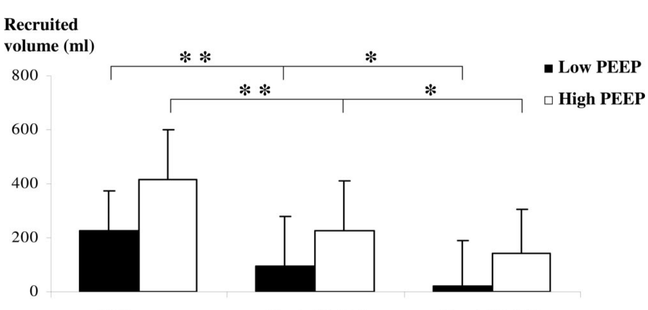

Fig. 4. Comparison of methods for evaluating positive end-expiratory pressure (PEEP) recruitment. The quasi–static compliance method, evaluated with tidal volumes of 400 ml (quasi-static compliance [C_{qST}], V_T400) and 700 ml (C_{qST}, V_T700), underestimated alveolar recruitment compared with the pressure–volume (P-V) curve method. Recruitment was compared with two PEEP levels. ** P < 0.01 between the two methods (with both tidal volumes of 400 and 700 ml) and * P < 0.05 between the two tidal volumes by the quasi-static method, by one-way analysis of variance and Bonferroni *post hoc* analysis.

Classification of ARDS

Whether the cause of ARDS was pulmonary or extrapulmonary could not be determined in 26 (37%) of our 71 patients because of mixed or uncertain origin. Although the retrospective design may have contributed to make classification difficult, the large proportion of unclassified patients suggests that errors or uncertainties in classification may be common. Several studies reported differences between pulmonary ARDS and extrapulmonary ARDS in patients with early-stage disease.[18] However, results among studies are conflicting, perhaps in part to the existence of cases of mixed origin and to errors in discriminating between pulmonary and extrapulmonary ARDS.[19] In a recent study, Esteban *et al.*[20] compared the clinical criteria for ARDS developed at the American-European Consensus Conference with autopsy findings.[1] The accuracy of the clinical criteria was moderate and was lower in patients with pulmonary risk factors than in patients with extrapulmonary risk factors.[20] These findings suggest that clinical misclassification may be common, most notably in patients with pulmonary or mixed ARDS. Gattinoni *et al.*[9] did not report difficulties in separating patients with pulmonary *versus* extrapulmonary ARDS. All but one of their patients with pulmonary ARDS had diffuse pneumonia, and most of those with extrapulmonary ARDS had abdominal sepsis.[9] These causes may not cover the entire spectrum of patients treated for ARDS in the intensive care unit.

Potential for Alveolar Recruitment and Timing of the Evaluation

Most of the patients studied by Gattinoni *et al.*[9] had very early–stage disease, with a time from symptom onset shorter than 72 h in most cases. Grasso *et al.*[8] reported that differences in chest wall mechanics according to the stage of ARDS influenced the potential for alveolar recruitment. Although the patients in our study had later-stage disease, 39 of the 71 (55%) had an early stage of ARDS. Among them, we found no further differences in alveolar recruitment across the three ARDS groups.

This finding has major implications for clinical practice. Although we did not determine functional residual capacity, data from other groups[16,21,22] suggest that lung volume may usually be in the 1,500- to 2,000-ml range. Therefore, the potential for recruitment may be approximately 15–20% of the lung volume on average.

P-V Curve and Abdominal Pressure

We used P-V curves of the total respiratory system, which can be used to explore lung mechanics and to measure alveolar recruitment. This method is easily and routinely performed at the bedside to optimize the PEEP level. We did not assess the influence of the chest wall on the respiratory system,[23] which can be substantial in patients with major abdominal distension and severe alterations in chest wall compliance.[4,24]

Measurement of Recruitment Using Quasi–Static Compliance from P-V Curves

The following differences regarding the measurement of alveolar recruitment using static compliance method may explain some contradictory results.

First, Gattinoni *et al.*[9] evaluated recruitment above the end-expiratory lung volume measured at zero end-expiratory pressure, using a closed-circuit helium dilution method. However, the authors did not measure end-expiratory lung volume at PEEP, and recruitment was calculated using static compliance. Although we did not measure end-expiratory lung volume, the volume above the end-expiratory lung volume at ZEEP (considered as the reference or zero value) was estimated during a passive expiration from PEEP to zero end-expiratory pressure. From this zero value, we also calculated recruitment induced by PEEP using the static compliance method. Indeed, P-V curves allow the measurement of alveolar recruitment without the need to measure end-expiratory lung volume. Second, Gattinoni *et al.*[9] calculated static compliance during occlusion maneuvers allowing elimination of the resistive pressure of the lung and to measure elastic pressure only. We measured this quasi–static compliance from P-V curves performed with a low flow to minimize resistive pressure. Moreover, when using the automated low-flow technique, the estimated resistive pressure of the respiratory system was subtracted from the measured pressure.

Third, the P-V curves in our study were obtained using two different methods. The multiple-occlusions method was more often used than the low-flow inflation method in patients with extrapulmonary ARDS. However, several studies showed that the P-V curves were similar with these two methods.[15,25]

P-V Curve Method versus *Static Compliance Method*

It has been suggested that alveolar recruitment may occur when PEEP induces an increase in static compliance.[26] However, there are several limitations to alveolar recruitment evaluation using the static compliance method. First, PEEP induces recruitment even when static compliance remains unchanged[10,27] or decreases.[3,6,12,28] Compared with the P-V curve method, the static compliance method can substantially underestimate alveolar recruitment because it does not take into account the sinusoidal shape of the P-V curve of the respiratory system (fig. 2). Therefore, underestimation may be greatest when the sinusoidal shape of the P-V curve is more marked. Gattinoni *et al.*[9] found no recruitment with 15 cm H_2O of PEEP in patients with pulmonary ARDS. We believe that static compliance method may be unreliable for evaluating respiratory system elastance and PEEP-induced recruitment. Therefore, when the same investigators used computed tomography to measure recruitment, they found that PEEP induced reaeration of the lung in patients with pulmonary ARDS.[29,30] More recently, Gattinoni *et al.*[31] evaluated the percentage of potentially recruitable lung indicated by computed tomography. They found that most of patients exhibiting a high potential for recruitment had ARDS caused by pneumonia, suggesting that the use of higher PEEP levels could be appropriate in these patients.

Computed tomographic morphologic features may differ between pulmonary and extrapulmonary ARDS.[32] However, the computed tomographic appearance does not consistently reflect the origin of ARDS.[33] Moreover, Rouby *et al.*[34] found that patients with diffuse attenuations on computed tomographic scans had a higher incidence of pulmonary ARDS than patients with lobar attenuations, and that PEEP induced marked alveolar recruitment in the group with diffuse attenuations. They concluded that alveolar recruitment induced by PEEP was affected by lung morphology rather than by the cause of ARDS.[17]

Conclusion

After a few days of mechanical ventilation, PEEP-induced alveolar recruitment seems independent of the underlying cause of ARDS. Therefore, in our study, potential for alveolar recruitment was as good in the patients with pulmonary ARDS as in those with extrapulmonary ARDS. Decisions about the PEEP level or the use of recruitment techniques during mechanical ventilation should not be based on the origin of ARDS. Static compliance systematically underestimates alveolar recruitment and cannot be used to evaluate PEEP-related alveolar recruitment.

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