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Relationship between ventilatory settings and barotrauma in the acute respiratory distress syndrome

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Abstract *Objective:* High pressures or volumes may increase the risk of barotrauma in the acute respiratory distress syndrome (ARDS). *Methods:* The first part of the study analyzed data from a prospective trial of two ventilation strategies in 116 patients with ARDS retrospectively, and ventilatory pressures and volumes were compared in patients with or without pneumothorax. The second part consisted of a literature analysis of prospective trials (14 clinical studies, 2270 patients) describing incidence and risk factors for barotrauma in ARDS patients, and mean values of ventilatory parameters were plotted against incidence of barotrauma. *Results:* In our clinical trial comparing two tidal volumes, 15 patients (12.3%) developed pneumothorax. There was no significant difference in any pressure or volume between these patients and the rest of the population, including end-inspiratory plateau pressure (P_{plat}), driving pressure (P_{plat}-PEEP), respiratory rate and compliance. Multiple trauma was more frequent among patients with pneumothorax (27%) than in those without (7%). Duration of mechanical ventilation tended to be longer with pneumothorax. In the literature review, the incidence of barotrauma varied between 0% and 49%, and correlated strongly with P_{plat}, with a high incidence above 35 cmH_2O, and with compliance, with a high incidence below 30 ml/cmH_2O. *Conclusion:* Clinical studies maintaining P_{plat} lower than 35 cmH_2O found no apparent relationship between ventilatory parameters and pneumothorax. Analysis of the literature suggests a correlation when patients receive mechanical ventilation with P_{plat} levels exceeding 35 cmH_2O.

Keywords Barotrauma · Pneumothorax · Acute respiratory distress syndrome · Mechanical ventilation

Introduction

Although life sustaining, mechanical ventilation may be deleterious for the lungs. Barotrauma and overdistension have been attributed to the use of high ventilatory pressures and volumes [1, 2] and may be responsible for morbidity and mortality. In patients with the acute respiratory distress syndrome (ARDS) the incidence of pneumothorax or barotrauma has been shown to range between zero [3] and more than 76% [4]. In ARDS, traditional tidal volumes (V_T; 10–15 ml/kg) may result in overdistension and high pressures because only a small aerated lung receives the total ventilation [5, 6]. This may contribute to damage in lung parenchyma. Based on these pathophysiological understandings, new ventilation strategies have been designed during the past decade, with the intent to reduce ventilator-induced lung injury in ARDS. Reduction in V_T and plateau pressure (P_{plat}) have been proposed and have recently been shown to have a strong impact on mortality [7, 8]. Although it is reasonable to think that lowering V_T could also lead to reduction in barotrauma [3, 7, 9], this has not been confirmed, except in the study by Amato et al. [7]. A study performed on a large database of ARDS patients found no relationship between ventilatory settings and the occurrence of air leaks [10]. In this study, however, no measurement of P_{plat} or driving pressure (the difference between P_{plat} and positive end-expiratory pressure) was available, and a relatively short period was used for assessing ventilatory pressures. Lastly, the recent ARDS network study found a difference in mortality but with no difference in barotrauma [11]. Because of these contradictory findings, we looked for the relationship between barotrauma and mechanical ventilatory settings in two ways.

We first retrospectively analyzed the database of our multicenter randomized study comparing two settings of V_T and P_{plat} [11] to determine whether the ventilatory parameters used in patients who subsequently developed pneumothorax differed from those of patients who did not develop barotrauma. Second, we performed an analysis of literature reporting the incidence and risk factors for barotrauma in ventilated patients with ARDS or at risk for ARDS and plotted the mean values of ventilatory parameters against incidence of barotrauma.

Methods

Definition of the ARDS database

The details of our prospective randomized trial can be found in the original paper [11]. In brief, patients with ARDS for 72 h or less, regardless of initial cause, were randomly assigned to receive conventional or pressure-limited ventilation. The ARDS was defined as evidence of diffuse bilateral infiltrates on chest radiography, hypoxemia requiring mechanical ventilation with minimum fraction of inspired oxygen (FIO_2) at 0.5 for more than 24 h, a Lung Injury Score [12] above 2.5, and no evidence of left ventricular failure. Patients were enrolled in the study between January 1994 and September 1996. Patients with severe organ failure other than respiratory failure, as defined by Knaus et al. [13], were not included, nor were those needing high levels of vasopressive agents or with preexisting chronic disease using the definitions of the Acute Physiology and Chronic Health Evaluation II and Simplified Acute Physiology Score II systems [14, 15] or other comorbidities. Patients were randomized to receive conventional or P_{plat} limited ventilation. Conventional ventilation was defined as volume-targeted (assist-control) ventilation, with a V_T of 10 ml/kg body weight or above (the upper limit allowed was 15 ml/kg, but the mean setting was 10.7 ml/kg), and a respiratory rate adjusted to maintain the arterial carbon dioxide tension ($PaCO_2$) between 38 and 42 mmHg. The ratio of inspiration to expiration was never higher than 1. Plateau-pressure limited ventilation was also defined as assist-control ventilation, but with V_T primarily titrated to maintain the end-inspiratory P_{plat} at or below 25 cmH_2O; P_{plat} was measured after a 2-s pause when patients were relaxed and not coughing or moving. V_T was maintained below 10 ml/kg but not lower than 6 ml/kg or 300 ml of V_T, irrespective of P_{plat}, as a safety limit to avoid excessive hypoventilation. V_T could be increased up to a P_{plat} of 30 cmH_2O if FIO_2 was at 0.9 or above, if reduced chest compliance was suspected, or if major acidosis was present (pH below 7.05). If pH decreased below 7.05, a careful titration using sodium bicarbonate was recommended. Positive end-expiratory pressure (PEEP) was set as in the conventional group. In both groups PEEP was set at the optimal level determined after a "PEEP trial" checking the greatest improvement in oxygenation or the first level allowing the ratio PaO_2/FIO_2 to be above 200 mmHg without worsening hemodynamics. In both groups body weight was defined as actual body weight minus the estimated weight gain due to water and salt retention, which is frequently present in septic patients.

Barotrauma was restricted to pneumothorax requiring chest tube drainage. Pneumothorax was identified on chest radiography obtained at baseline and then once daily and for clinical indications.

Analysis of the database

Having identified patients who had developed at least one episode of pneumothorax, we compared the characteristics of mechanical ventilation in these patients (PNO^+) to those without pneumothorax ($PNO^–$). The following measurements, recorded once daily until the 14th day and then once weekly until discontinuation of mechanical ventilation, discharge from intensive care unit (ICU), or death, were available: total external PEEP, peak inspiratory pressure (PIP), mean airway pressure (MAP), end-inspiratory P_{plat}, V_T, V_T indexed to body weight, and respiratory rate. We also calculated the driving pressure defined as difference between P_{plat} and PEEP, and the static "effective" compliance.

We compared the highest pressures and volumes at any time in the first 5 days of mechanical ventilation in patients without pneumothorax, with the highest pressures and volumes in the 48-h period before the event in those with pneumothorax. We also compared the mean values of all ventilatory parameters in the 5-day period among patients without pneumothorax, with those in the whole period preceding its occurrence in patients sustaining pneumothorax.

Data recorded on the day of the episode of pneumothorax were not taken into account because it was not possible to distinguish whether they had been recorded before or after pneumothorax occurrence. Nevertheless, when these values were included in the analysis, they did not affect the results.

As shown in Fig. 1, all episodes of pneumothorax but two occurred within the first 8 days of the study, with a median of

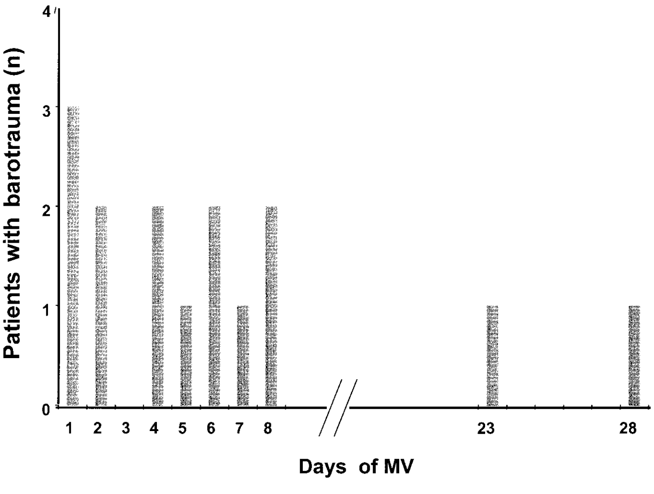

Fig. 1 Number of patients developing pneumothorax according to the duration of mechanical ventilation (*MV*) in our randomized trial [11]

4 days. We therefore considered for the control group (PNO^{-}) the first 5 days under mechanical ventilation as the most relevant period to be considered for analysis of ventilatory parameters. Indeed, the database may have been insufficient to analyze cases with very late occurrence of pneumothorax.

The Mann-Whitney *U* test was used to compare values in patients with, and in those without pneumothorax. Binary variables were compared using the χ^2 test. Data are presented as mean ±standard deviation.

Literature review

Identification of studies

A computerized search was conducted to identify appropriate literature on the topic of barotrauma risk factors in ARDS ventilated patients. We searched for studies published in English language using Medline for the years 1966–1999. The following terms were used in the search: (a) barotrauma and ARDS, (b) pneumothorax and ARDS. Other sources of relevant articles were review articles.

Selection of studies

Two of us (M.B., G.T.) independently reviewed the Medline reference list and clearly irrelevant articles were discarded. If the title or the abstract suggested any possibility of relevance, the article was retrieved. The following inclusion criteria were used to select studies:

- Design: prospective trials or consecutive patients including at least 20 patients
- Patients: patients under mechanical ventilation with or at high risk of acute lung injury (ALI) or ARDS
- Interventions: primary research involving incidence and risk factors of barotrauma
- Availability of the mean values of measured ventilatory parameters (pressures, volumes, etc)

Some studies required an intervention such as extracting the ARDS patient subgroup or calculating mean values of some respiratory physiological parameters. We also looked for other relevant articles by examining the related articles provided by the Medline search and those referenced in the articles found. They also tried to include other key words than “barotrauma” or “pneumothorax” but were not able to retrieve more appropriate papers. We decided to also include studies enrolling patients with or at high risk of ALI or ARDS because the rationale was similar [16].

Data collection

A data collection form was completed for all studies meeting the inclusion criteria. Abstracted data included: title, authors, year of publication, source, population studied, patient demographics, outcomes, follow-up timing and duration, interventions (mainly mechanical ventilation pattern), incidence of barotrauma, mechanical ventilation and physiological respiratory parameters.

Data analysis

Reports were analyzed for mean values of ventilatory parameters in each patient subset according to mechanical ventilation pattern. Values of each parameter were then plotted on graphs according to the respective incidence of barotrauma reported in the study and are presented on Figs. 2, 3, 4, 5, 6, 7, and 8. Linear regression analyses were performed, and r^2 values are given.

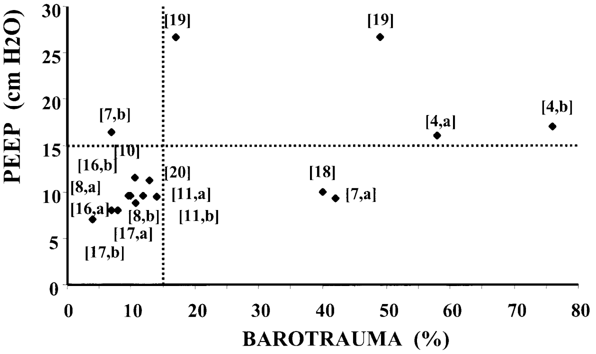

Fig. 2 Distribution of mean values of positive end-expiratory pressure (*PEEP*) and incidences of barotrauma in studies identified by the literature search, with cutoff set at 15 cmH2O for PEEP and at 15% for incidence of barotrauma. Each data point represents the incidence of barotrauma versus the mean value of PEEP used in one study or in one group of patients when two different ventilatory strategies were used in one study, recorded during the first 24 h, and is identified by its reference number (see also Table 3 for the subgroups). Note the lack of correlation between PEEP and incidence of barotrauma (r^2=0.17)

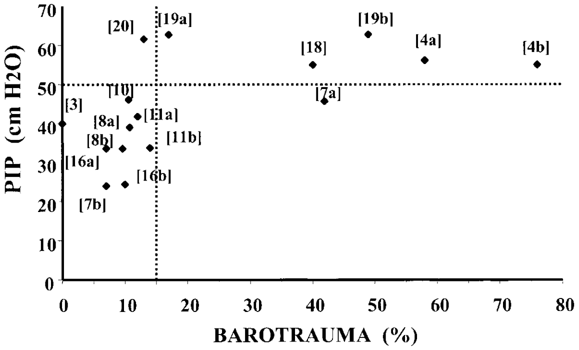

Fig. 3 Same presentation than in Fig. 2 for peak inspiratory pressure (*PIP*), with cutoff set at 50 cmH2O for PIP and at 15% for incidence of barotrauma. Note a weak correlation between PIP and incidence of barotrauma (r^2=0.32)

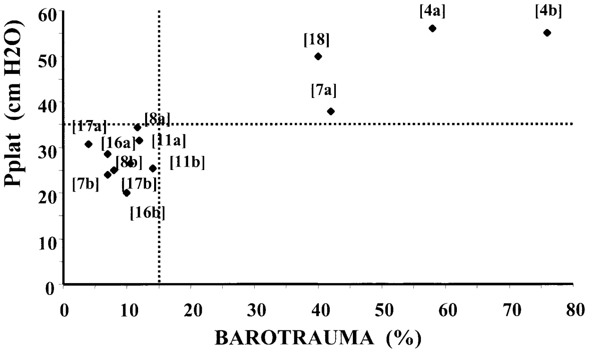

Fig. 4 Same presentation than in Fig. 2 for end-inspiratory plateau pressure (*Pplat*), with cutoff set at 35 cmH_2O for Pplat and at 15% for incidence of barotrauma. Note the strong correlation between Pplat and incidence of barotrauma (r^2=0.84)

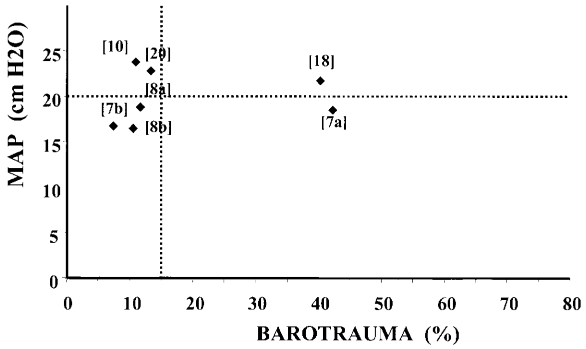

Fig. 5 Same presentation than in Fig. 2 for mean airway pressure (*MAP*), with cutoff set at 20 cmH_2O for MAP and at 15% for incidence of barotrauma. Note the lack of correlation between MAP and incidence of barotrauma (r^2=0.01)

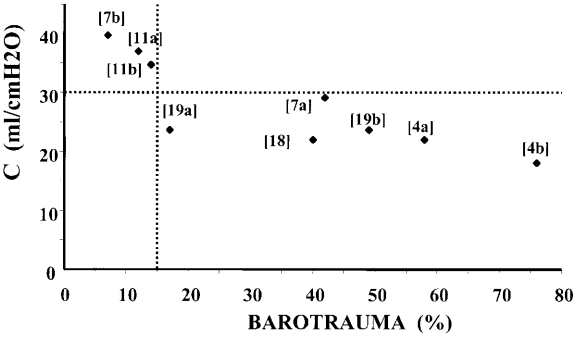

Fig. 8 Same presentation than in Fig. 2 for static compliance (*C*), with cutoff set at 30 ml/cmH_2O for C and at 15% for incidence of barotrauma. Note the strong correlation between C and incidence of barotrauma (r^2=0.70)

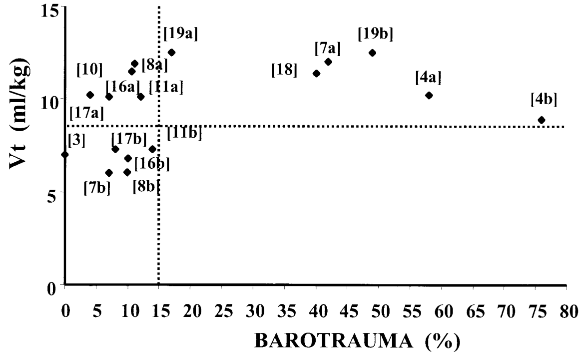

Fig. 6 Same presentation than in Fig. 2 for tidal volume (V_T ml/kg), with cutoff set at 8 ml/kg for V_T and at 15% for incidence of barotrauma. Note the lack of correlation between V_T and incidence of barotrauma (r^2=0.15)

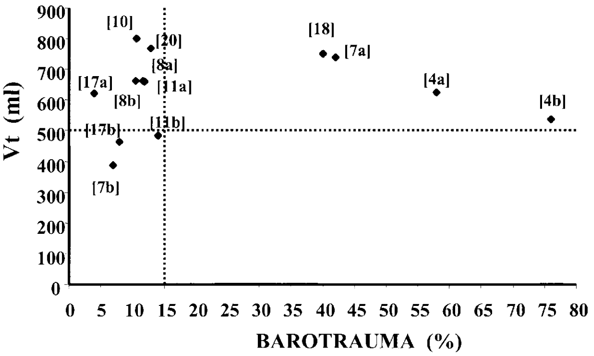

Fig. 7 Same presentation than in Fig. 2 for tidal volume (V_T ml), with cutoff set at 500 ml for V_T and at 15% for incidence of barotrauma. Note the lack of correlation between V_T and incidence of barotrauma (r^2=0.01)

Results

Retrospective analysis of our controlled trial

The overall incidence of pneumothorax was 12.3% (15/116), and reached 13.8% (8/58) in the pressure-limited ventilation group and 12.1% (7/58) in the conventional ventilation group [11]. Baseline demographic and clinical characteristics of the study population, according to the presence or absence of pneumothorax, are shown in Table 1. The mean time to development of pneumothorax was 7.1±7.9 days (range 1–28). If the two "outliers" patients (13%) who experienced pneumothorax, respectively on days 23 and 28 of the study period were not included, this mean value was kept at 4.2±2.6 days in the 13 remaining patients (range 1–8; Fig. 1). Patients developing pneumothorax had more pronounced hypoxemia on admission and had a slightly but nonsignificantly longer time under mechanical ventilation (*p*=0.06). Table 2 shows respective mean values of ventilatory parameters. There were no significant differences in any pressures or volumes among the two groups of patients. Compliance, driving pressure, and respiratory rate were also similar. Multiple trauma as a cause of ARDS was more frequent in PNO^+ patients, but no difference was found regarding pneumonia or immunosuppression (Table 2). Need for paralysis was also similar. Mortality rate was not significantly different between PNO^+ and PNO^- patients.

Review of ARDS studies

Selection

There have been many reports of studies analyzing incidence and risk factors for barotrauma in ventilated patients, but very few reported mean measured values of ventilatory pressures and set volumes. We identified 224

Table 1 Baseline demographic and clinical characteristics of the patients with or without pneumothorax in our randomized controlled trial comparing two tidal volumes [11] (*PNO* pneumothorax, *SAPS* II Simplified Acute Physiology Score II, *APACHE II* Acute Physiology And Chronic Health Evaluation II, *LIS* Lung Injury Score, *D ICU-MV* duration from admission to intensive care unit to initiation of mechanical ventilation, *D MV-ARDS* duration from initiation of mechanical ventilation to onset of ARDS; *D ARDS-INC* duration from onset of ARDS to inclusion in the study, PaO_2 arterial oxygen tension, $PaCO_2$ arterial carbon dioxide tension, FIO_2 fraction of inspired oxygen, PaO_2/FIO_2 ratio of arterial oxygen tension to fraction of inspired oxygen, *Trauma* patients with multiple trauma, *Immuno* patients with immunosuppression, *Pneumonia* patients with pneumonia at the onset of ARDS, *Others* remaining patients, *DMV* whole duration of mechanical ventilation)

	PNO$^-$ (*n*=101)	PNO$^+$ (*n*=15)	*p*
Sex: M/F	59/49	7/8	0.56
SAPS II	37.2±12.1	34.0±13.3	0.43
APACHE II	18.2±8.1	16.7±7.2	0.57
LIS	2.96±0.29	3.0±0.30	0.98
D ICU-MV (days)	0.1±2.9	0.2±2.8	0.21
D MV-ARDS (day)	2.3±5.3	2.3±3.5	0.37
D ARDS-INC (day)	1.1±0.8	1.3±0.9	0.43
PaO_2 (mmHg)	104±44	79±19	0.03
$PaCO_2$ (mmHg)	51±15	48±12	0.74
FIO_2	0.7±0.2	0.7±0.2	0.22
PaO_2/FIO_2 (mmHg)	153±67	125±37	0.16
pH	7.34±0.11	7.35±0.08	0.95
Group			
Trauma	7 (7%)	4 (27%)	0.04
Immuno	6 (6%)	1 (7%)	NS
Pneumonia	54 (53%)	7 (46%)	NS
Others	34 (34%)	3 (20%)	NS
Mortality	40 (40%)	9 (60%)	NS
DMV (day)	21.2±17.8	29.5±20.1	0.06

Table 2 Ventilatory variables according to the presence or absence of pneumothorax in our randomized controlled trial comparing two tidal volumes [11] (*PNO* pneumothorax, *PIP* inspiratory peak pressure, *PEEP* positive end-expiratory pressure level, P_{plat} end-inspiratory plateau pressure, *Dp* driving pressure, *C* static effective compliance at inclusion to the study, *RR* respiratory rate value, V_T tidal volume)

	PNO$^-$ (*n*=101)	PNO$^+$ (*n*=15)	*p*
PIP mean (cmH_2O)	37.6±9.4	38.9±10.3	0.67
PIP max (cmH_2O)	40.9±9.7	39.8±10	0.64
PEEP mean (cmH_2O)	9.5±2.8	10.3±2	0.16
PEEP max (cmH_2O)	10.3±2.8	10.4±2.8	0.95
P_{plat} mean (cmH_2O)	28.1±6.4	29.6±7.8	0.41
P_{plat} max (cmH_2O)	30.6±7.1	30.2±7.9	1.00
Dp mean (cmH_2O)	18.6±6.1	19.3±7.3	0.76
Dp max (cmH_2O)	21±6.8	20.7±7.8	0.73
C (ml/cmH_2O)	37±16.4	33.7±13.7	0.5
RR mean (c/min)	18.7±2.8	18.6±2.9	0.77
RR max (c/min)	19.7±3.5	19±3.6	0.36
V_T mean (ml)	574±160	554±112	0.83
V_T max (ml)	611±169	567±119	0.43
V_T mean (ml/kg)	8.7±2.2	8.3±2.1	0.45
V_T max (ml/kg)	9.2±2.4	8.5±2.1	0.28

studies between the years 1976 and 1999 in the initial Medline literature search. Two independent reviewers selected 19 papers that appeared relevant from this search. Review of recent publications and citations in books and review articles yielded only four additional articles for relevance assessment. Of the 23 assessed articles 14 met the inclusion criteria, and only 11 were valuable with an overall number of 2270 subjects (Table 3); three studies were excluded because the relevant information could not be retrieved from the published paper.

Description of eligible studies

The included papers were all published during the 1990s. "Risk factors for barotrauma" was not always the primary outcome studied in these reports. Several trials studied the effect of reducing V_T [3, 4, 7, 8, 10, 11, 16, 17] comparing new approaches or protective ventilation strategies to more conventional ones. One study compared conventional ventilation and a pressure limited ventilation associated to extracorporeal CO_2 removal [4]. In these studies we differentiated subgroups according to mechanical ventilation pattern. One study analyzed barotrauma risk factors in a large group of ventilated patients [18], but we used only the data from patients with the ARDS (42 of 168 patients). Another trial investigated mortality in ARDS patients treated with high-level PEEP [19], and the remaining investigated barotrauma in patients with ALI [20].

Relationship between ventilatory settings and barotrauma

The results are displayed on Figs. 2, 3, 4, 5, 6, 7, and 8 for the recorded pressures, volumes, and compliance. We differentiated studies with a "low" incidence of barotrauma and those with a "high" incidence of barotrauma and looked for the value of the observed parameter that could best discriminate the two incidences. We arbitrarily selected the threshold of 15% to distinguish low from high incidence of barotrauma because our literature search identified two kind of studies. In the first group of studies the incidence of barotrauma was below 15%, while in the other group the incidence was much higher, with no studies between 15% and 38%. The only exception was the study by Di Russo et al. [19], which reported two different values for the incidence of barotrauma: taking into account all episodes, the incidence was in the high range. However, they also reported a lower incidence (17%) of pneumothorax after exclusion of episodes not related to mechanical ventilation (e.g., catheter, trauma). This differentiation was not reported in the other studies, but we indicate these two numbers on the graphs. We could have taken any threshold be-

Table 3 Characteristics of series included in the review of ARDS studies (*PNO* pneumothorax, *ARDS* acute respiratory distress syndrome, *risk ARDS* patients at high risk of ARDS, *ALI* acute lung injury, *CONV* conventional mechanical ventilation, *PROT* protective mechanical ventilation strategy, *CPPV* continuous positive pressure ventilation, *PCIRV* pressure-controlled inverted-ratio ventilation, *LFPPV* low-frequency positive pressure ventilation, *ECCO$_2$R* extracorporeal CO_2 removal)

Reference	*n*	Patients	MV pattern	Barotrauma (%)	PNO (%)	APACHE II
Hickling et al. [3]	53	ARDS	CONV	0	0	25
Morris et al. [4]	19	ARDS	CPPV, PCIRV	58	–	17
	21	ARDS	LFPPV, ECCO$_2$R	76	–	18
Amato et al. [7]	24	ARDS	CONV	42	–	27
	29	ARDS	PROT	7	–	28
Network ARDS [8]	432	ALI	PROT	10	–	–
	429	ALI	CONV	11	–	–
Weg et al. [10]	725	ARDS	CONV	10.6	5.9	–
Brochard et al. [11]	58	ARDS	CONV	12	12	–
	58	ARDS	PROT	14	14	–
Stewart et al. [16]	60	At risk ARDS	CONV	7	–	21.5
	60	At risk ARDS	PROT	10	–	22.4
Brower et al. [17]	26	ARDS	CONV	4	–	–
	26	ARDS	PROT	8	–	–
Gammon et al. [18]	42	ARDS	CONV	40	40	18.6
Di Russo et al. [19]	67	ARDS	CONV	49	41	–
	41	ARDS	CONV	17	7	–
Schnapp et al. [20]	100	ALI	CONV	13	9	–

tween 15% and 35%, but we thought it important to identify the studies with a "low" incidence of barotrauma, likely to be independent of mechanical ventilation, as suggested by the results of Weg et al. [10]. A strong relationship (more than 80% of the data points are in the lower left quadrant or the upper right quadrant) were found for peak pressure (limit at 50 cmH_2O), P_{plat} (limit at 35 cmH_2O; 100% of the data points) and compliance (limit at 30 ml/cmH_2O; 100% of the data points). For these two parameters a strong correlation existed with barotrauma. Respiratory rate is not reported on a graph but had no relationship with barotrauma.

Discussion

Similar to the study by Weg et al. [10], the analysis of the data from our randomized trial was unable to identify in this series of patients with early ARDS any relationship between barotrauma and high ventilatory pressures or volumes. In our analysis of literature, however, the incidence of barotrauma was markedly higher in groups of patients ventilated with mean values for end-inspiratory P_{plat} above 35 cmH_2O and in whom lung compliance was below 30 ml/cmH_2O.

Experimental studies have shown that high PIP values near 45–50 cmH_2O [1, 21], or even lower, about 30 cmH_2O [22], induce lesions related to alveolar overinflation. In patients with ARDS parenchymal destruction related to hyperinflation has been observed in pathological examination and seemed more frequent when patients received high volumes or pressures [23].

Several recent studies, including our own, comparing low V_T with conventional ventilation in ARDS have failed to demonstrate any reduction in mortality and barotrauma when low V_T values were used [11, 16, 17]. It is noteworthy that in these three studies, V_T values were relatively "low" in both groups (V_T around 10–11 ml/kg and P_{plat} below 35 cmH_2O in the conventional arms). This feature may have played a major role in the absence of difference in mortality and barotrauma between the two groups.

Our literature review found two ranges of incidence for barotrauma in the studies, a low range, as in the studies by Brochard et al. [11] and Weg et al. [10], and a high range, as in other studies [4, 18]. In the case of a low incidence of barotrauma neither the study by Weg et al. [10] nor our own analysis found any relationship with ventilatory parameters, which suggests that barotrauma could have been more related to the underlying process than to the ventilatory settings. We found a higher incidence of barotrauma in trauma patients, as already suggested by others [20]. An explanation for the low incidence of barotrauma in this group of patients with ARDS may therefore be that, irrespective of the mechanical ventilation pattern, mean pressures did not exceed 30–35 cmH_2O P_{plat} in contrast to studies with high incidence of barotrauma.

We also studied the driving pressure, i.e., P_{plat} minus PEEP, which may better reflect the tidal distending pressure, considered to reflect the opening and closing forces present during tidal ventilation with closed or filled alveoli. There was no correlation with barotrauma. There were no differences when data were analyzed according to gender, or severity of general scoring system, but there were more trauma patients and trends for longer duration of mechanical ventilation in the pneumothorax group. Although we had a smaller group of patients with pneumothorax, our results agree with those of Weg et al. [10] in a large series of 725 patients, in which end-inspiratory P_{plat} and driving pressure were not available. These findings suggest that a low rate of barotrauma can be achieved keeping P_{plat} below 35 cmH_2O as recommended by the American-European consensus conference [24]. We can hypothesize that when P_{plat} is kept below 35 cmH_2O, there is a low but unavoidable rate of pneumothorax, not related to mechanical ventilation but resulting from other pulmonary conditions, such as previous lung alteration [25] or the cause of the ARDS.

We found that a low compliance (below 30 ml/cmH_2O) was associated with a high incidence of barotrauma. This is an interesting finding because compliance measured during tidal ventilation is likely to both reflect the severity of lung disease and to depend on the ventilatory settings. High V_T values exceeding the upper inflection point of the pressure-volume curve of the respiratory system [26] cause compliance to decrease, as well as hyperinflation [27, 28]. On the other hand, insufficient PEEP level could also contribute to low compliance values measured over the V_T range. Therefore the dependence of barotrauma on compliance may indicate that the combination of severe abnormalities in respiratory mechanics and inappropriately high pressures or volumes and/or, to a lower extent, insufficient PEEP levels, are necessary to generate barotrauma.

One potential important limitation of our design is the use of mean values of ventilatory parameters for the analysis of the published trials. We did not collect patients' individual values for all selected trials. One cause of error may come from an asymmetric distribution of the variables around the mean. In our multicenter trial [11] the distribution of variables around the mean was symmetrical. This was not tested for the other studies. The other cause of error comes from the size of the standard deviation. A large standard deviation would imply that a few individuals were treated with much higher values than the mean reported value, which could not be considered as a threshold. Other factors that could affect the relationship between P_{plat} and barotrauma include chest wall compliance, variable spontaneous respiratory activity, and type and duration of underlying disease. Furthermore, airway pressure is often not monitored, for instance, during manual insufflation or following tracheal suctioning. These situations expose one to only brief and not sustained variation in airway pressure. In fact, all the above factors are likely to cloud the relationship between the ventilatory parameters and the occurrence of barotrauma. Despite all these limitations and possible confounding factors it is striking to observe such a strong relationship between P_{plat} and barotrauma. One strength of this analysis, which may explain these results, is that all data were collected prospectively in the studies. Although this type of analysis does not allow making firm recommendations for individual ventilator settings, it does give some light on the pathophysiology of this process.

In conclusion, barotrauma in patients ventilated with ARDS seems nowadays to be uncommon. Its incidence can vary with severity and distribution of lung disease, but mechanical ventilation pattern can account for the high incidences viewed in the literature, especially when end-inspiratory P_{plat} was kept above the threshold point of 35 cmH_2O.

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