Effects of sustained inflation and postinflation positive end-expiratory pressure in acute respiratory distress syndrome: Focusing on pulmonary and extrapulmonary forms*

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Objective: To investigate whether the response to sustained inflation and postinflation positive end-expiratory pressure varies between acute respiratory distress syndrome with pulmonary ($ARDS_p$) and extrapulmonary origin ($ARDS_{exp}$).

Design: Prospective clinical study.

Setting: Multidisciplinary intensive care unit in a university hospital.

Patients: A total of 11 patients with $ARDS_p$ and 13 patients with $ARDS_{exp}$.

Interventions: A 7 ml/kg tidal volume, 12–15 breaths/min respiratory rate, and an inspiratory/expiratory ratio of 1:2 was used during baseline ventilation. Positive end-expiratory pressure levels were set according to the decision of the primary physician. Sustained inflation was performed by 45 cm H_2O continuous positive airway pressure for 30 secs. Postinflation positive end-expiratory pressure was titrated decrementally, starting from a level of 20 cm H_2O to keep the peripheral oxygen saturation between 92% and 95%. FIO_2 was decreased, and baseline tidal volume, respiratory rate, inspiratory/expiratory ratio were maintained unchanged throughout the study period.

Measurements and Main Results: Blood gas, airway pressure, and hemodynamic measurements were performed at the following time points: at baseline and at 15 mins, 1 hr, 4 hrs, and 6 hrs after sustained inflation. After sustained inflation, the PaO_2/FIO_2 ratio improved in all of the patients both in $ARDS_p$ and $ARDS_{exp}$. However, the PaO_2/FIO_2 ratio increased to >200 in four $ARDS_p$ patients (36%) and in seven $ARDS_{exp}$ patients (54%). In two of those $ARDS_p$ patients, the PaO_2/FIO_2 ratio was found to be <200, whereas none of the $ARDS_{exp}$ patients revealed PaO_2/FIO_2 ratios of <200 at the 6-hr measurement. Postinflation positive end-expiratory pressure levels were set at 16.7 ± 2.3 cm H_2O in $ARDS_{exp}$ and 15.6 ± 2.5 cm H_2O in $ARDS_p$. The change in PaO_2/FIO_2 ratios was found statistically significant in patients with $ARDS_{exp}$ (p = .0001) and with $ARDS_p$ (p = .008). Respiratory system compliance increased in $ARDS_{exp}$ patients (p = .02), whereas the change in $ARDS_p$ was not statistically significant.

Conclusions: Sustained inflation followed by high levels of postinflation positive end-expiratory pressure provided an increase in respiratory system compliance in $ARDS_{exp}$; however, arterial oxygenation improved in both ARDS forms. (Crit Care Med 2003; 31:738–744)

KEY WORDS: extrapulmonary acute respiratory distress syndrome; pulmonary acute respiratory distress syndrome; sustained inflation; positive end-expiratory pressure; gas exchange; respiratory system compliance

Ventilator associated lung injury has been considered an important complication of mechanical ventilation in acute lung injury and acute respiratory distress syndrome (ARDS). Several studies have shown that the amplitude of cyclic changes in lung volume may be responsible for the development of edema through the generation of high shear forces between open and closed lung units in ARDS (1–3). Furthermore, repetitive opening and closing of unstable lung units has been reported to activate pulmonary and systemic inflammatory mediators (4, 5) and to cause bacterial translocation from the lung to systemic circulation (6, 7).

In theory, high positive end-expiratory pressure (PEEP)/low tidal volume strategies are proposed to avoid injurious cycles of closure and reopening because small tidal volumes limit high airway pressures and PEEP counterbalances the increased tendency for airway closure (8–10). The improvement in survival of patients with acute respiratory failure by using high levels of PEEP was first reported by Douglas and Downs (11). In recent years, Amato et al. (10) demonstrated improved outcome by using a lung protective mechanical ventilation strategy with small tidal volume that also employed lung recruitment maneuvers plus PEEP levels set according to a pressure-volume curve to try to keep the recruited lung open. Beneficial effects of low tidal volume ventilation on minimizing ventilator associated lung injury and reducing mortality was supported by the study of the National Institutes of Health (12). However, effects of recruitment maneuvers and high PEEP levels on ventilator associated lung injury and mortality rate were not further investigated in the randomized clinical studies using low tidal volumes in patients with ARDS (13–15).

Recruitment maneuvers have been proven to be an effective way to achieve alveolar recruitment and improve oxygenation, not only in animal experiments but also in patients with ARDS (16–18). However, the most effective method of

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lung recruitment has not yet been determined. Intermittent sighs (17, 19), episodic increases of PEEP (20), and sustained inflation maneuvers that achieve total lung capacity (16, 21) have been used in different studies. Identification of the ideal level of PEEP sufficient enough to keep the lung open after a recruitment maneuver has also been questioned.

It has also been proposed that the ability of PEEP to keep re-expanded units open at end-expiration will depend on patient factors, including the cause and stage of disease. In a recent study, Gattinoni et al. (22) stated that the recruiting effect of PEEP was more remarkable when the underlying pathology is extrapulmonary and when interstitial edema and alveolar collapse is prevalent in the early phase of ARDS. However, in that study, measurements of lung and chest wall mechanics were not linked to gas exchange data.

The aim of our study was to investigate the effects of sustained inflation associated with a high postinflation PEEP on gas exchange and respiratory compliance in patients with extrapulmonary and pulmonary ARDS ($ARDS_{exp}$ and $ARDS_p$, respectively). We hypothesized that our ventilatory strategy should provide a more prominent improvement in arterial oxygenation in ARDS caused by an indirect insult than ARDS caused by a direct insult (22).

MATERIAL AND METHODS

Study Population. This investigation was approved by the Institutional Ethics Committee of Istanbul Medical Faculty, and informed consent was obtained from the next of kin of the patients before inclusion in the study. Patients who had pneumothorax, necrotizing pneumonitis, or structural chest wall abnormalities were not included in the study population.

A total of 24 consecutive patients with ARDS of varying pathogeneses were studied. All subjects were enrolled in the study within 24 hrs of onset of ARDS. The diagnosis of ARDS was based on the criteria proposed by the American-European Consensus Conference on ARDS (23): acute onset, presence of hypoxemia (Pa_{O_2}/F_{IO_2} of <200, regardless of positive end expiratory pressure level), diffuse bilateral infiltrates seen on frontal chest radiograph, and absence of congestive heart failure.

Assignment of the patients to the pulmonary (n = 11) and extrapulmonary (n = 13) groups was based on history, clinical presentation, computed tomographic scans and microbiological tests. Assignment of a patient to an ARDS subgroup required the agreement of five intensive care unit physicians.

If the physicians did not reach an agreement on the pathogenesis of the lung insult, those patients were not included in the study. None of the $ARDS_p$ patients had positive blood cultures. Three of the $ARDS_{exp}$ patients who had positive airway secretion cultures also had positive blood cultures. We limited our study to the early phase (within 24 hrs) of the disease to rule out the overlap of two insults. Acute Physiology and Chronic Health Evaluation Score II (APACHE II), Multiple Organ Failure score, and the Lung Injury Score defined by Murray et al. (24) were recorded on the day of the study.

Baseline Ventilation. Patients were ventilated using a Servo 300 ventilator (Siemens-Elema, Solna, Sweden). Pressure-regulated volume-control ventilation with 7 mL/kg tidal volume, 12–15 breaths/min respiratory rate, and inspiratory/expiratory ratio of 1:2 was defined as baseline ventilation. PEEP levels were set according to the decision of the primary physician.

Sustained Inflation. Patients were sedated with fentanyl and midazolam and paralyzed with vecuronium bromide throughout the study period. Mean arterial pressure and central venous pressure were continuously monitored and recorded (Horizon 2000, Mennen Medical, Rehovot, Israel). During sustained inflation, 45 cm H_2O continuous positive airway pressure was applied for 30 secs while keeping F_{IO_2} unchanged. After sustained inflation at 45 cm H_2O, baseline tidal volume, respiratory rate, and inspiratory/expiratory ratio were maintained unchanged.

PEEP Selection After Sustained Inflation. PEEP selection was performed clinically. After sustained inflation, PEEP was decreased immediately to 20 cm H_2O. Then, F_{IO_2} was reduced until peripheral oxygen saturation (Sp_{O_2}) levels were maintained between 92% and 95%. If peak inspiratory pressure exceeded 45 cm H_2O with the initial level of 20 cm H_2O PEEP, PEEP was reduced until peak inspiratory pressure was ≤45 cm H_2O. If initial peak inspiratory pressure was ≤45 cm H_2O, postinflation PEEP was determined by decreasing PEEP gradually, starting from the level of 20 cm H_2O. PEEP was reduced by 1 cm H_2O decrements, aiming to keep the Sp_{O_2} between 92% and 95%. If Sp_{O_2} levels fell to <92%, postinflation PEEP level was then set at the next to the last value without performing a second sustained inflation to reverse any derecruitment that might have occurred. After the selection of postinflation PEEP, F_{IO_2} was further decreased if the Pa_{O_2}/F_{IO_2} ratio exceeded 200 in blood gas analyses performed during the 6-hr follow-up period.

Measurements. After the stabilization of ventilatory variables, arterial blood gas analyses were performed (ABL 700, Radiometer, Copenhagen, Denmark) and peak, mean, and plateau airway pressures were recorded from the ventilator at baseline and at 15 mins, 1 hr, 4 hrs, and 6 hrs after the recruitment maneuver. End-inspiratory hold maneuvers were performed to measure plateau airway pressure. Total PEEP ($PEEP_t$) was measured with an end-expiratory hold maneuver for 5 secs. Static lung compliance of the respiratory system (Cst) (Tidal volume/plateau airway pressure − $PEEP_t$) were also calculated. To minimize the airway pressure drops during aspiration of tracheal secretions, patients were connected to a closed aspiration system. If disconnections occurred, sustained inflation was repeated.

Statistical Analysis. Data are given as the mean ± SD. Wilcoxon's test was used to compare hemodynamic, respiratory, and gas exchange variables between baseline measurements and measurements recorded after sustained inflation. Intergroup comparisons were made by Mann-Whitney *U* tests. Sex distribution was analyzed by using Fisher's exact test. Intragroup variations in hemodynamic, respiratory, and gas exchange variables over time were analyzed using Friedman's analysis of variance. A p value of <.05 was considered statistically significant.

RESULTS

Over the study period, 31 adult patients were diagnosed as having ARDS. Seven patients were excluded from the study because of pneumothorax (n = 2), necrotizing pneumonitis (n = 1), a time lapse of >24 hrs since onset of ARDS (n = 2), and disagreement on the pathogenesis of lung insult (n = 2).

Admission diagnosis and the clinical entry data are summarized in Table 1. Lung Injury Score and APACHE II scores were similar, whereas, because of the design of the study, the Multiple Organ Failure score was found to be different between the groups ($p = .03$). Tidal volumes ranged between 320 and 550 mL, with a mean value of 440 ± 80 mL in $ARDS_p$. In $ARDS_{exp}$, tidal volumes ranged between 300 and 650 mL, with a mean value of 457 ± 119 mL. The difference between tidal volumes were not significant ($p = .9$). The mean respiratory frequency was 13 ± 1.5 breaths/min in $ARDS_p$ and 13 ± 0.9 breaths/min in $ARDS_{exp}$ ($p = .6$).

Before the application of sustained inflation, baseline PEEP levels ranged between 5 and 15 cm H_2O, with a mean value of 9.6 ± 3 cm H_2O in $ARDS_p$. Postinflation PEEP levels ranged between 10 and 18 cm H_2O, with a mean value of 15.6 ± 2.5 cm H_2O in $ARDS_p$. The difference between baseline PEEP and postinflation PEEP levels were statistically significant ($p = .002$) in $ARDS_p$. In $ARDS_{exp}$,

Table 1. Diagnosis and clinical characteristics of patients

	$ARDS_p$ (n = 11)	$ARDS_{exp}$ (n = 13)	p Value
Underlying diseases (n)	Thoracic trauma/pneumonia (4), primary pneumonia (6), aspiration (1)	Wound infection-sepsis (1), abdominal sepsis (11), liver transplantation (1)	
Age, yrs	57 ± 19	44 ± 15	.09
Sex (M/F)	6 / 5	7 / 6	1
APACHE II score	16 ± 7	13.5 ± 9.5	.3
MOF score	5.2 ± 4.4	7 ± 2.2	.03
LIS	2.5 ± 0.4	2.8 ± 0.4	.3

ARDS, acute respiratory distress syndrome; $ARDS_p$, pulmonary ARDS; $ARDS_{exp}$, extrapulmonary ARDS; APACHE II, Acute Physiology and Chronic Health Evaluation II; MOF, Multiple Organ Failure; LIS, Lung Injury Score.

baseline PEEP levels ranged between 5 and 15 cm H_2O, with a mean value of 10.3 ± 3.6 cm H_2O. Postinflation PEEP levels ranged between 12 and 20 cm H_2O, with a mean value of 16.7 ± 2.3cm H_2O in $ARDS_{exp}$. The difference between baseline PEEP and postinflation PEEP levels in $ARDS_{exp}$ were statistically significant (p = .001). Baseline PEEP levels and postinflation PEEP levels were found to be similar between the groups (p = .56 and p = .42, respectively).

Hemodynamic variables did not change significantly in either groups, except for central venous pressure, which had a statistically significant increase over time in $ARDS_{exp}$ (p = .02) (Table 2). Airway pressures are given in Table 3. Peak inspiratory pressure and mean and plateau airway pressures increased after application of PEEP in both groups. Cst, Pa_{O_2}/F_{IO_2} ratio, F_{IO_2}, pH, and Pa_{CO_2} values are shown in Table 4. Baseline Cst values were found to be similar between the groups (p = .7). Cst increased significantly in $ARDS_{exp}$ patients, whereas the change in $ARDS_p$ patients was not statistically significant. Cst increased in all of the patients in $ARDS_{exp}$, whereas an increase in Cst was observed in four of the patients in $ARDS_p$.

The Pa_{O_2}/F_{IO_2} ratio improved in all of the patients, both in pulmonary and extrapulmonary ARDS groups (Fig. 1). After sustained inflation, the Pa_{O_2}/F_{IO_2} ratio increased to >200 in four $ARDS_p$ patients (36%) and in seven $ARDS_{exp}$ patients (54%). In two of those $ARDS_p$ patients, the Pa_{O_2}/F_{IO_2} ratio was found to be <200, whereas none of the $ARDS_{exp}$ patients revealed Pa_{O_2}/F_{IO_2} ratios of <200 at the 6-hr measurement. $ARDS_p$ patients who demonstrated an improvement in Cst were not the same as those who had the best responses in Pa_{O_2}/F_{IO_2} ratio.

The decrease in F_{IO_2} was statistically significant in both ARDS forms. A further significant decrease in F_{IO_2} occurred over the 6 hrs after the recruitment maneuver (p = .002 in $ARDS_p$ and p = .0001 in $ARDS_{exp}$). F_{IO_2} was tapered in seven $ARDS_p$ patients (64%) and 11 $ARDS_{exp}$ patients (85%). Pa_{CO_2} and pH did not reveal statistically significant changes in either group of patients.

No significant adverse effects occurred, and sustained inflations were well tolerated. The 30-sec sustained inflation was completed in all patients. We observed bradycardia in two $ARDS_p$ patients and in one $ARDS_{exp}$ patient, which did not cause a decrease in mean arterial pressure of >20% of baseline values and resolved spontaneously after the inflation was terminated. Barotrauma was not observed in any of the patients.

DISCUSSION

The major finding of our study is that a sustained inflation of 45 cm H_2O for 30 secs and application of a postinflation PEEP of approximately 16 cm H_2O can improve arterial oxygenation in ARDS of both pulmonary and extrapulmonary origin. We observed that static respiratory compliance increased only in patients with $ARDS_{exp}$ in response to our ventilation strategy.

Sustained Inflation and Gas Exchange. The concept of recruiting the lungs and preventing alveolar instability and derecruitment is a well-accepted ventilatory strategy in ARDS. Various forms of recruitment maneuvers have been established in human or animal subjects (10, 17, 18, 25–27). Based on these data, sustained inflation within the range of 30–45 cm H_2O applied for 15–30 secs have been found effective in improving oxygenation and pulmonary mechanics by recruitment of collapsed alveolar units. However, the adequate pressure level and the duration of sustained inflations have not been settled yet. In our study, we applied an inflation pressure of 45 cm H_2O for 30 secs and achieved an improvement in arterial oxygenation of patients with ARDS.

It was previously shown that lung recruitability might be influenced by the nature of the lung insult itself. Gattinoni et al. (22) proposed that patients with $ARDS_p$ had substantial lung consolidation with minimal recruitment with PEEP. Patients with $ARDS_{exp}$, on the other hand, had alveolar edema and atelectasis that was more responsive to recruitment with PEEP. Pelosi et al. (17) also stated that the potential for sigh-induced lung recruitment was different between $ARDS_p$ and $ARDS_{exp}$. The increase in arterial oxygen tension and the decrease in venous admixture were approximately 35 and 55 mm Hg and 3% and 18% in $ARDS_p$ and $ARDS_{exp}$, respectively, in that study. The authors concluded that $ARDS_{exp}$ seemed to be more responsive to sighs.

The difference in the nature of two different types of ARDS was also illustrated by the results of the present study. Patients with $ARDS_{exp}$ demonstrated favorable arterial oxygenation and respiratory compliance responses to sustained inflation. However, patients with $ARDS_p$ did not show an improvement in respiratory compliance. Interestingly, although the increases were less striking than in $ARDS_{exp}$ patients, mean Pa_{O_2}/F_{IO_2} ratios of $ARDS_p$ patients increased significantly after sustained inflation. Patients with $ARDS_p$ who had the best responses in Pa_{O_2}/F_{IO_2} ratio were not the same as those who demonstrated an improvement in respiratory compliance. This finding supports the role of mechanisms in addition to lung recruitment in the improvement of gas exchange induced by PEEP. As mentioned previously, redistribution of pulmonary blood flow can account, at least in part, for changes in arterial oxygenation without a significant change in lung mechanics (28, 29). The decrease in blood flow to shunt regions as a consequence of a general reduction in cardiac output (30, 31) has also been considered as a mechanism improving gas exchange. In our study conditions, we also speculate that the recruitment of atelectatic regions surrounding the consolidated areas in patients with $ARDS_p$ could also play a role in the improvement of arterial oxygenation, at least in certain cases.

PEEP Selection and Derecruitment. Although recruitment maneuvers are intended to open collapsed lung units,

Table 2. Hemodynamic parameters

	Baseline	15 mins	1 hr	4 hrs	6 hrs	ANOVA p Value
MAP, mm Hg						
$ARDS_p$	93 ± 13	85 ± 16	86 ± 17	88 ± 11	92 ± 11	.3
$ARDS_{exp}$	87 ± 17	83 ± 17	84 ± 16	86 ± 13	88 ± 11	.6
CVP, mm Hg						
$ARDS_p$	13.4 ± 3.5	13 ± 4	13.4 ± 4	15 ± 2.8	15 ± 2	.2
$ARDS_{exp}$	13.6 ± 4.7	15 ± 5.3	15.2 ± 4.6	14 ± 5.3	15.6 ± 4.4	.02

ANOVA, analysis of variance; ARDS, acute respiratory distress syndrome; $ARDS_p$, pulmonary ARDS; $ARDS_{exp}$, extrapulmonary ARDS; MAP, mean arterial pressure; CVP, central venous pressure. Data are expressed as mean ± SD.

Table 3. Pulmonary mechanics

	Baseline	15 mins	1 hr	4 hrs	6 hrs	ANOVA p Value
Ppeak, cm H_2O						
$ARDS_p$	34 ± 5.5	40 ± 6.4[a]	40 ± 5.5[b]	39.8 ± 5[b]	39.5 ± 5[b]	.01
$ARDS_{exp}$	35 ± 6.4	38.3 ± 5.2[a]	39.5 ± 5.5[c]	39.3 ± 5[b]	39 ± 5[b]	.009
Pmean, cm H_2O						
$ARDS_p$	16.4 ± 3	21.6 ± 2.2[a]	22 ± 3[b]	21.7 ± 3.5[b]	22 ± 3.4[b]	<.0001
$ARDS_{exp}$	17 ± 3	22 ± 3[a]	22.4 ± 3[a]	22.4 ± 2.7[a]	22 ± 3[a]	<.0001
Pplateau, cm H_2O						
$ARDS_p$	27.2 ± 4.0	34 ± 4.4[b]	34.1 ± 3.6[b]	34.3 ± 2.7[a]	33.7 ± 4.1[a]	.0002
$ARDS_{exp}$	28.6 ± 5.6	32.1 ± 5.1[c]	32 ± 5.1[c]	32 ± 4.9[b]	31.3 ± 4.8[c]	.03
Cst (mL/cm H_2O)						
$ARDS_p$	39.4 ± 10.7	36.7 ± 9.8	35.9 ± 8.4	35.7 ± 8.8	36.6 ± 8.7	.9
$ARDS_{exp}$	39.0 ± 14.5	45.5 ± 24	46.8 ± 20.5[b]	45.6 ± 14.6[c]	47.2 ± 18.8[c]	.02

ANOVA, analysis of variance; P_{peak}, peak airway pressure; ARDS, acute respiratory distress syndrome; $ARDS_p$, pulmonary ARDS; $ARDS_{exp}$, extrapulmonary ARDS; Pmean, mean airway pressure; Pplateau, plateau airway pressure; Cst, static compliance. Data are expressed as mean ± SD.

[a] $p < 0.001$ when compared with baseline values; [b] $p < 0.01$ when compared with baseline values; [c] $p < 0.05$ when compared with baseline values.

Table 4. Gas exchange

	Baseline	15 mins	1 hr	4 hrs	6 hrs	ANOVA p Value
PaO_2/FiO_2						
$ARDS_p$	105 ± 32.2	173 ± 75.2[a]	181 ± 77[b]	174 ± 90[a]	161 ± 57[c]	.008
$ARDS_{exp}$	121 ± 47	210 ± 118[a]	214 ± 97[a]	223 ± 88[c]	236 ± 93[c]	.0001
FiO_2						
$ARDS_p$	0.8 ± 0.18	0.74 ± 0.18	0.7 ± 0.17	0.64 ± 0.15[b]	0.62 ± 0.15[b]	.0006
$ARDS_{exp}$	0.82 ± 0.21	0.77 ± 0.22	0.66 ± 0.18[a]	0.6 ± 0.17[c]	0.56 ± 0.13[c]	<.0001
pH						
$ARDS_p$	7.36 ± 0.05	7.35 ± 0.08	7.37 ± 0.08	7.38 ± 0.09	7.38 ± 0.07	.8
$ARDS_{exp}$	7.34 ± 0.05	7.34 ± 0.06	7.35 ± 0.05	7.36 ± 0.07	7.36 ± 0.07	.9
$PaCO$, mm Hg						
$ARDS_p$	46.7 ± 8.8	47.7 ± 10.7	45.1 ± 9.8	44.6 ± 9.7	45 ± 10	.9
$ARDS_{exp}$	47.0 ± 10.4	47.7 ± 10.6	47.4 ± 11.5	45.7 ± 12	44.8 ± 10	.4

ANOVA, analysis of variance; ARDS, acute respiratory distress; $ARDS_p$, pulmonary ARDS; $ARDS_{exp}$, extrapulmonary ARDS.

[a] $p < 0.01$ when compared with baseline values; [b] $p < 0.05$ when compared with baseline values; [c] $p < 0.01$ when compared with baseline values. Data are expressed as mean ± SD.

sufficiently high PEEP levels are needed to maintain unstable lung units open while avoiding excessive stretching and hemodynamic impairment. The importance of selecting an appropriate postrecruitment maintenance pressure was established by Kolton et al. (32). However, the criterion for the selection of this "open-lung" PEEP remains to be determined. In a recent study, the beneficial effects of an inflation pressure of 30–45 cm H_2O was noted to be lost during the 4-hr follow-up in 28% of the patients. This was reported to be the result of using a PEEP level insufficient to maintain recruitment (18). Fujino et al. (19) reported that repetitive high-pressure recruitment maneuvers would have been unnecessary if the lung had been kept recruited by using 20 cm H_2O PEEP between the maneuvers.

In the present study, the PEEP that would most likely hold the recruited units open, providing satisfactory oxygenation, was defined to be the postinflation PEEP. The postinflation PEEP was determined with stepwise decrements, starting from a level of 20 cm H_2O PEEP. During this decremental PEEP selection, our goal was to achieve an acceptable oxygenation while maintaining peak alveolar pressures at <45 cm H_2O. The PEEP values that we applied after sustained inflation were slightly higher than PEEP values used in the study of Pelosi et al. (17) and quite similar to the PEEP used in study by Amato et al (8). Inasmuch as oxygenation increases were sustained over the 6 hr period, our data provide support for the use of oxygenation as a surrogate bedside monitor of the ability of a selected PEEP level to maintain alveolar recruitment after a sustained inflation maneuver.

Pelosi et al. (17) used "trial" PEEP (14 ± 2 cm H_2O), which was selected according to arterial oxygenation in patients with ARDS, and observed that the improvement in both gas exchange and mechanical changes induced by sighing returned to baseline within 30 mins after interruption of sighing. They suggested that derecruitment occurred mainly as a function of resorption atelectasis and lack of adequate PEEP levels. In contrast, in our study, gas exchange was maintained and actually continued to improve over the 6-hr period after recruitment. Because derecruitment may occur as a consequence of gas resorption, the composition of inspired gas will play a role in maintaining the recruitment effect (33). In our study, the inspired oxygen concentration was tapered in accordance with the individual response of oxygenation to the ventilatory strategy. The maintenance of the satisfactory gas exchange may be attributed to the relatively high PEEP levels, combined with decreasing FiO_2 levels.

In the present study, relatively low tidal volumes were kept constant throughout the follow-up period. It was previously shown that the use of low tidal volumes could induce a progressive decrease in compliance, indicating a time-dependent derecruitment, which could be counterbalanced with higher levels of

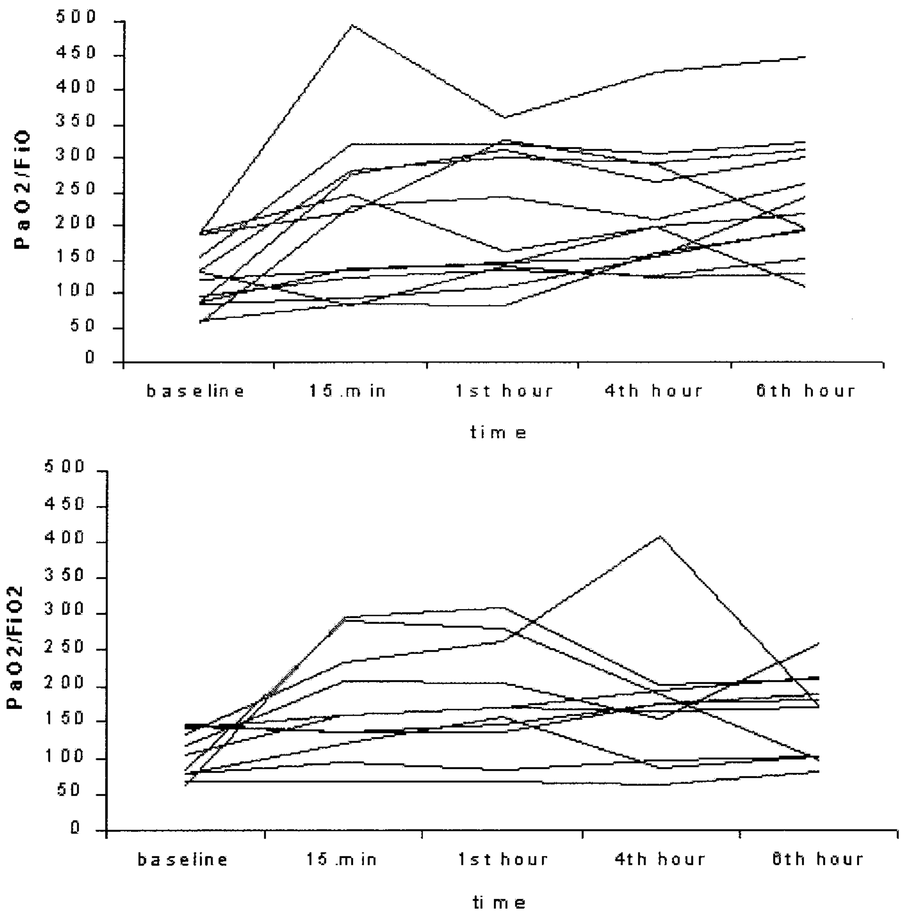

Figure 1. The change in Pa_{O_2}/FI_{O_2} ratios in extrapulmonary acute respiratory distress syndrome (*top*) and pulmonary acute respiratory distress syndrome (*bottom*).

Sustained inflation followed by high levels of postinflation positive end-expiratory pressure provided an increase in respiratory system compliance in extrapulmonary acute respiratory distress syndrome; however, arterial oxygenation improved in both pulmonary and extrapulmonary forms of acute respiratory distress syndrome.

PEEP (34, 35). It is difficult to ascertain whether the maintenance of recruitment was an effect of the increased plateau pressures or high postinflation PEEP levels preventing end-expiratory collapse. In two recent studies, it was demonstrated that both end-inspiratory and expiratory pressures influence the amount of end-expiratory lung collapse in clinical (36) and experimental conditions (37).

Our data may be questioned for the method of postinflation PEEP selection. In animal models, ventilatory-induced lung injury is greatly reduced by setting the PEEP level slightly higher than the lower inflection point of the pressure-volume curve and using an appropriate tidal volume to avoid overdistension (38). This strategy has also been used in patients with ARDS, and promising results have been reported (10, 39). However, the best method of determining the level of PEEP needed to prevent end-expiratory collapse has been questioned in recent years. Several studies suggest that setting PEEP based on the lower inflection point of the inflation pressure-volume curve does not prevent derecruitment of the lung (17, 40–42). In the study of Pelosi et al. (17), derecruitment occurred even with the clinically selected trial PEEP that was found to be higher than the lower inflection point PEEP.

In a mathematical model of ARDS, Hickling (40) reported that the maximum pressure-volume slope during a decremental PEEP trial after a recruitment maneuver could be a useful approach to select open-lung PEEP. In a decremental PEEP trial, Maggiore et al. (42) showed that 5 cm H_2O PEEP decrements were too large because major alveolar derecruitment was evident even at high baseline PEEP levels of 15 or 20 cm H_2O. They demonstrated that alveolar closure occurs over a wide range of pressures, and the lower inflection point is a poor predictor of closing pressure. We therefore preferred to set the postinflation PEEP by stepwise decrements of 1 cm H_2O in accordance with peripheral oxygen saturation, which proved a very easy technique to apply at the bedside.

Static Respiratory Compliance. As it was noted previously, an increase in respiratory compliance is a reliable predictor of recruitment of collapsed lung units, whereas a decrease in compliance occurs as a result of excessive hyperinflation (43). In our study, we observed a consistent increase in respiratory compliance in all of the patients with $ARDS_{exp}$, indicating the recruitment of previously unventilated airspaces by sustained inflation. Maintenance of this increase in respiratory compliance should be the consequence of using a postinflation PEEP level of 16.7 ± 2.3 cm H_2O in the follow-up period. In contrast, respiratory compliance was unaltered or decreased in most of the patients with $ARDS_p$ in response to our ventilation strategy. Because the compliance of the respiratory system was not partitioned in our study, it is difficult to ascertain which component of the respiratory system was responsible for the difference between two groups of patients. Despite this limitation, it can be stated that sustained inflation had a different mechanical impact on the lungs in the $ARDS_p$ and $ARDS_{exp}$ patients. This finding has been previously supported by Gattinoni et al. (22), who demonstrated opposite responses in lung mechanics of patients with $ARDS_p$ and $ARDS_{exp}$ to increasing levels of PEEP in a study that did not involve recruitment maneuvers. In that study, increase in the lung component of the respiratory system elastance in patients with pulmonary ARDS by using PEEP levels up to 15 cm H_2O was explained by the stretching phenomena. Worsening of respiratory system compliance in our study might indicate overdistention of already open alveoli in some of the patients with ARDS of pulmonary origin; however, arterial oxygen and CO_2 levels in those patients did not support this consideration. A possible explanation of this conflict could be the improvement in ventilation/perfusion mismatch, which might be induced by regional differences in lung recruitment.

Limitations. In our study, there are some limitations that should be noted. A limited number of patients in our study population had pulmonary artery catheters. Measurement of changes in cardiac output and pulmonary shunt would have enabled us to assess the contributions of changes in pulmonary flow and in lung recruitment. Static respiratory system compliance was not partitioned in our study. Measuring chest wall and lung compliance would be more informative in determining which component of the respiratory system compliance changed in $ARDS_{exp}$ and $ARDS_p$ patients. Moreover, measurement of lung volumes would also be helpful in interpretation of the effects of our ventilation strategy on lung recruitment and derecruitment. However, one strength of our methodology is that it demonstrates an approach to the achievement and maintenance of alveolar recruitment that requires only standard intensive care unit equipment used appropriately at the bedside.

During postinflation PEEP selection, PEEP was reduced until peripheral oxygen saturation started to fall below the value that was achieved after sustained inflation. If we had performed a second sustained inflation maneuver and then set postinflation PEEP to next to the last value, even larger improvements in PaO_2/FIO_2 may have been observed. In conclusion, this study demonstrated the successful use of high-pressure recruitment maneuver and relatively high levels of postinflation PEEP to provide an improvement in arterial oxygenation in both pulmonary and extrapulmonary ARDS.

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REFERENCES

1. Lachmann B: Open up the lung and keep the lung open. *Intensive Care Med* 1992; 18:319–321
2. Sandhar BK, Niblet DJ, Argiras EP, et al: Effects of positive end-expiratory pressure on hyaline membrane formation in a rabbit model of the neonatal respiratory distress syndrome. *Intensive Care Med* 1988; 14:538–546
3. Muscedere JG, Mullen JBM, Gan K, et al: Tidal ventilation at low airway pressures can augment lung injury. *Am J Respir Crit Care Med* 1994; 149:1327–1334
4. Tremblay L, Valenza F, Ribeiro S, et al: Injurious ventilatory strategies increase cytokines and C-fos m-RNA expression in an isolated rat lung model. *J Clin Invest* 1997; 99:944–952
5. Takata M, Aabe J, Tanaka H, et al: Intraalveolar expression of tumour necrosis factor-α gene during conventional and high-frequency ventilation. *Am J Respir Crit Care Med* 1997; 156:272–279
6. Nahum A, Hoyt J, Schmitz L, et al: Effects of mechanical ventilation strategy on dissemination of intratracheally instilled *Escherichia coli* in dogs. *Crit Care Med* 1997; 25:1733–1743
7. Verbrugge SJC, Sorm V, Veen A, et al: Lung overinflation without positive end-expiratory pressure promotes bacteremia after experimental *Klebsiella pneumonia* inoculation. *Intensive Care Med* 1998; 24:172–177
8. Amato MB, Barbas CS, Medeiros DM, et al: Beneficial effects of the “open lung approach” with low distending pressures in acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1995; 152:1835–1846
9. Papadakos PJ, Apostokaols MJ: High-inflation and positive end-expiratory pressure: Injurious to the lung? Yes. *Crit Care Clin* 1996; 12:627–634
10. Amato MB, Barbas CS, Medeiros DM, et al: Effect of a protective-ventilation strategy on mortality in acute respiratory distress syndrome. *N Engl J Med* 1998; 338:347–354
11. Douglas ME, Downs JB: Pulmonary function following severe acute respiratory failure and high levels of positive end-expiratory pressure. *Chest* 1977; 71:18–23
12. Acute Respiratory Distress Syndrome Network: Ventilation with lower tidal volume as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000; 342:1301–1308
13. Stewart TE, Meade MO, Cook DJ, et al: Evaluation of a ventilation strategy to prevent barotrauma in patients with high risk for acute respiratory distress syndrome. *N Engl J Med* 1998; 338:355–361
14. Brochard L, Roudot-Thoroval E, Roupie E, et al: Tidal volume reduction for prevention of ventilator-induced lung injury in the acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1998; 158:1831–1838
15. Brower RG, Shanholtz CB, Fessler HE, et al: Randomized trial of small tidal volumes ventilation in ARDS. *Crit Care Med* 1999; 27:1492–1498
16. Rimensberger PC, Pache JC, McKerlie C, et al: Lung recruitment and lung volume maintenance: A strategy for improving oxygenation and preventing lung injury during both conventional and high-frequency oscillation. *Intensive Care Med* 2000; 26:745–755
17. Pelosi P, Cadringher P, Bottino N, et al: Sigh in acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1999; 159:872–880
18. Lapinsky SE, Aubin M, Metha S, et al: Safety and efficacy of a sustained inflation for alveolar recruitment in acute respiratory distress syndrome. *Intensive Care Med* 1999; 25:1297–1301
19. Fujino Y, Goddon S, Dolhnikoff M, et al: Repetitive high-pressure recruitment maneuvers required to maximally recruit lung in a sheep model of acute respiratory distress syndrome. *Crit Care Med* 2001; 29:1579–1586
20. Foti G, Cereda M, Sparacino ME, et al: Effects of periodic lung recruitment maneuvers on gas exchange and respiratory mechanics in mechanically ventilated acute respiratory distress syndrome patients. *Intensive Care Med* 2000; 26:501–507
21. Walsh MC, Carlo WA: Sustained inflation during HFOV improves pulmonary mechanics and oxygenation. *J Appl Physiol* 1988; 65:368–372
22. Gattinoni L, Pelosi P, Suter PM, et al: Acute respiratory distress syndrome caused by pulmonary and extrapulmonary disease: Different syndromes? *Am J Respir Crit Care Med* 1998; 158:3–11
23. Bernard GR, Artigas A, Brigham KL, et al: The American-European Consensus Conference on ARDS: Definition, mechanisms, relevant outcomes and clinical trial coordination. *Am J Respir Crit Care Med* 1994; 149:818–824
24. Murray JF, Matthay MA, Luce JM, et al: An expanded definition of the adult respiratory distress syndrome. *Am Rev Respir Dis* 1988; 138:720–723
25. Bond DM, McAloon J, Froese AB: Sustained inflations improve respiratory compliance during high-frequency oscillatory ventilation but not during large tidal volume positive-pressure ventilation in rabbits. *Crit Care Med* 1994; 22:1269–1277
26. Van der Kloot TE, Blanch L, Youngblood M, et al: Recruitment maneuvers in three experimental models of lung injury: Effects on lung volume and gas exchange. *Am J Respir Crit Care Med* 2000; 161:1485–1494
27. Cakar N, Van der Kloot TE, Youngblood M, et al: Oxygenation response to a recruitment maneuver during supine and prone positions in an oleic acid-induced lung injury model. *Am J Respir Crit Care Med* 2000; 161:1949–1956
28. Falke KJ, Pontoppidan H, Kumar A, et al: Ventilation with positive end-expiratory pressure in acute lung disease. *J Clin Invest* 1972; 51:2315–2323
29. Ralph DD, Robertson TH, Weaver LJ, et al: Distribution of ventilation and perfusion during positive end-expiratory pressure in the adult respiratory distress syndrome. *Am J Respir Crit Care Med* 1985; 131:54–60
30. Dueck R, Wagner PD, West JB: Effects of

positive end-expiratory pressure on gas exchange in dogs with normal and edematous lungs. *Anesthesiology* 1977; 47:359–366
31. Dantzker DR, Brook CJ, Dehart P, et al: Ventilation-perfusion distributions in the adult respiratory distress syndrome. *Am Rev Respir Dis* 1979; 120:1039–1052
32. Kolton M, Cattran CB, Kent G, et al: Oxygenation during high-frequency ventilation compared with conventional mechanical ventilation in two models of lung injury. *Anesth Analg* 1982; 61:323–332
33. Dantzker DR, Wagner PD, West JB: Instability of lung units with low VA/Q ratios during O_2 breathing. *J Appl Physiol* 1975; 38: 886–895
34. Cereda M, Foti G, Musch G, et al: Positive end-expiratory pressure prevents the loss of respiratory compliance during low tidal volume ventilation in acute lung injury patients. *Chest* 1996; 109:480–485
35. Ranieri VM, Mascia L, Fiorev T, et al: Cardiorespiratory effects of positive end-expiratory pressure during progressive tidal volume reduction (permissive hypercapnia) in patients with acute respiratory distress syndrome. *Anesthesiology* 1995; 83:710–720
36. Crotti S, Mascheroni D, Caironi P, et al: Recruitment and derecruitment during acute respiratory failure: A clinical study. *Am J Respir Crit Care Med* 2001; 164:131–140
37. Pelosi P, Goldner M, McKibben A, et al: Recruitment and derecruitment during acute respiratory failure: An experimental study. *Am J Respir Crit Care Med* 2001; 164:122–130
38. Dreyfuss D, Saumon G: Ventilator-induced lung injury. *Am J Respir Crit Care Med* 1998; 157:294–323
39. Gattinoni L, Pesenti A, Avalli L, et al: Pressure-volume curve of total respiratory system in acute respiratory failure. *Am J Respir Crit Care Med* 1987; 136:730–736
40. Hickling KG: Best compliance during a decremental, but not incremental, positive end-expiratory pressure trial is related to open-lung positive end-expiratory pressure: A mathematical model of acute respiratory distressed syndrome lungs. *Am J Respir Crit Care Med* 2001; 163:69–78
41. Hickling KG: The pressure-volume curve is greatly modified by recruitment. *Am J Respir Crit Care Med* 1998; 158:194–202
42. Maggiore SM, Jonson B, Richard JC, et al: Alveolar derecruitment at decremental positive end-expiratory pressure levels in acute lung injury: Comparison with the lower inflection point, oxygenation and compliance. *Am J Respir Crit Care Med* 2001; 164:795–801
43. Ranieri VM, Eissa NT, Corbeil C, et al: Effect of PEEP on alveolar recruitment and gas exchange in ARDS patients. *Am J Respir Crit Care Med* 1991; 144:544–551