ARDSnet Ventilatory Protocol and Alveolar Hyperinflation

Role of Positive End-Expiratory Pressure

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***Rationale*: In patients with acute respiratory distress syndrome (ARDS), a focal distribution of loss of aeration in lung computed tomography predicts low potential for alveolar recruitment and susceptibility to alveolar hyperinflation with high levels of positive end-expiratory pressure (PEEP).**

***Objectives*: We tested the hypothesis that, in this cohort of patients, the table-based PEEP setting criteria of the National Heart, Lung, and Blood Institute's ARDS Network (ARDSnet) low tidal volume ventilatory protocol could induce tidal alveolar hyperinflation.**

***Methods*: In 15 patients, physiologic parameters and plasma inflammatory mediators were measured during two ventilatory strategies, applied randomly: the ARDSnet and the stress index strategy. The latter used the same ARDSnet ventilatory pattern except for the PEEP level, which was adjusted based on the stress index, a monitoring tool intended to quantify tidal alveolar hyperinflation and/or recruiting/derecruiting that occurs during constant-flow ventilation, on a breath-by-breath basis.**

***Measurements and Main Results*: In all patients, the stress index revealed alveolar hyperinflation during application of the ARDSnet strategy, and consequently, PEEP was significantly decreased ($P < 0.01$) to normalize the stress index value. Static lung elastance ($P = 0.01$), plasma concentrations of interleukin-6 ($P < 0.01$), interleukin-8 ($P = 0.031$), and soluble tumor necrosis factor receptor I ($P = 0.013$) were significantly lower during the stress index as compared with the ARDSnet strategy–guided ventilation.**

***Conclusions*: Alveolar hyperinflation in patients with focal ARDS ventilated with the ARDSnet protocol is attenuated by a physiologic approach to PEEP setting based on the stress index measurement.**

Keywords: acute lung injury; inflammatory response; mechanical ventilation; ventilator-induced lung injury

Mechanical ventilation can exacerbate the inflammatory response in patients with acute respiratory distress syndrome (ARDS) by inducing cyclic tidal alveolar hyperinflation and/or recruiting/derecruiting (1). Several protective ventilatory strategies have been proposed to minimize these forms of ventilator-induced micromechanical stress. A randomized multicenter study by the National Heart, Lung, and Blood Institute's ARDS Network (ARDSnet) comparing tidal volumes of 6 versus 12 ml/kg predicted body weight showed a significantly better survival in those individuals allocated to the low tidal volume arm (2). However, because the same positive end-expiratory pressure (PEEP) setting criteria (protocolized alternating increases of PEEP and inspired oxygen fraction [$F_{I_{O_2}}$]) were applied in both arms of the ARDSnet study, their impact in terms of lung protection remains unclear (3). Moreover, a more recent ARDSnet investigation (Assessment of Low Tidal Volume and Elevated End-Expiratory volume to Obviate Lung Injury [ALVEOLI] trial) (4), testing the effects on mortality of a "higher" PEEP titration table, did not show any improvement when compared with the original trial. A study by our group suggests, as a possible explanation of this result, that the table-based approach to the higher PEEP setting of the ALVEOLI study may have failed to induce a physiologic response in terms of alveolar recruitment in a significant group of patients (5).

Using computed tomography (CT), Gattinoni and coworkers have recently shown that the potential for alveolar recruitment is quite variable among patients with ARDS (6). Previously, the CT Scan ARDS study group classified ARDS into focal (36% of patients), diffuse (23%), and patchy (41%), based on the pattern of distribution of loss of aeration (7, 8), and showed that the chances of producing alveolar recruitment with PEEP can be predicted *a priori* using this classification (9). Accordingly, in patients with a focal distribution of loss of aeration (i.e., with atelectatic dependent lobes coexisting with aerated nondependent lobes), the use of high PEEP levels (15–20 cm H_2O) resulted in minimal alveolar recruitment in the dependent lobes but significant hyperinflation in the nondependent lung lobes (10).

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Mechanical ventilation may exacerbate lung injury in patients with acute respiratory distress syndrome (ARDS) causing tidal alveolar hyperinflation. The ARDSnet protective ventilatory protocol was intended to minimize hyperinflation by applying low tidal volumes.

What This Study Adds to the Field

We found evidence of alveolar hyperinflation in patients with focal ARDS ventilated with the ARDSnet protocol. Individual positive end-expiratory pressure titration based on the "stress index" monitoring reduced the risk of alveolar hyperinflation.

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In the present study, we tested the hypothesis that ventilation using the standardized ARDSnet PEEP–FI_{O_2} protocol would induce alveolar hyperinflation in patients with focal ARDS. Therefore, we compared in these patients the ARDSnet ventilatory strategy with an alternative strategy characterized by a more "physiologic" titration of PEEP, aimed at minimizing ventilator-induced tidal hyperinflation. To do so, we adjusted PEEP based on stress index monitoring, as recently proposed by De Perrot and colleagues and Ranieri and coworkers (11–13). The stress index is determined on a breath-by-breath basis during constant-flow ventilation by analyzing the shape of the inspiratory airway opening pressure curve. This approach assumes that, during constant-flow tidal inflation, the rate of change in airway opening pressure over time reflects the rate of change in elastance of the respiratory system (14). A recent CT study suggested that the stress index may accurately quantify the degree of tidal alveolar hyperinflation (15).

Parts of this study have previously been reported in abstract format (16).

METHODS

Additional details provided in the online supplement.

Patients with early ARDS (17), fulfilling the inclusion criteria of the ARDSnet protocol (2), were included in the study provided they had undergone a thoracic CT scan for clinical purposes in the preceding 24 hours that revealed a pattern of focal loss of aeration according to the CT Scan ARDS study group criteria (7, 9). The qualitative CT analysis was performed by two independent radiologists (G.A. and M.M.). The institutional review board for clinical studies approved the protocol, and written, informed consent was obtained from each patient or his or her next of kin before enrollment into the study.

Measurements

Static elastance (partitioned for respiratory system, chest wall, and lung), quasi-static pressure–volume curves of the respiratory system (low-flow technique), and PEEP-induced alveolar recruitment were measured as previously described (5).

The stress index was measured during constant-flow assist-control mechanical ventilation without changing the baseline ventilatory pattern, as previously described (11–13, 15) (further details are provided in the online supplement). Briefly, a computer program (ICU-LAB; KleisTEK, Bari, Italy) aided in identifying the steady part of the inspiratory flow and the corresponding portion of the airway opening pressure curve, and in fitting to the latter the following power equation:

$$\text{airway pressure} = a \cdot \text{inspiratory time}^{b} + c,$$

where the coefficient b ("stress index") describes the shape of the curve. For stress index values of less than 1, the curve presents a downward concavity suggesting a continuous decrease in elastance. For stress index values of higher than 1, the curve presents an upward concavity suggesting a continuous increase in elastance. Finally, for a stress index value equal to 1, the curve is straight, suggesting the absence of tidal variations in elastance (Figure 1). To suppress eventual spontaneous inspiratory efforts during the measurement, the baseline sedation level (Ramsay score 3–4) (18) could be briefly (10–15 min) increased to a Ramsay score of 5 during stress index measurements. No further increase in sedation or neuromuscular blockade was allowed to facilitate the stress measurement.

Invasive arterial pressure, heart rate, right atrial pressure, continuous cardiac output (via transesophageal Doppler, Cardio Q; Deltex Medical, Chichester, UK), and arterial blood gases (Rapid Lab 865; Bayer Diagnostics, Dublin, Ireland) were determined under each experimental condition.

Plasma concentrations of interleukin (IL)-6, IL-8, tumor necrosis factor (TNF)-α, and soluble TNF-α receptors I and II (sTNF-α RI and II) were measured with commercially available kits for solid-phase ELISAs (IL-6, IL-8, TNF-α; Bender Medical Systems, Vienna, Austria; sTNF-α RI and II; HyCult Biotechnology, Uden, The Netherlands).

Study Protocol

From the moment the diagnosis of ARDS was made all patients were ventilated following the ARDSnet protocol. During the study period of 24 hours, each patient was initially ventilated for 12 hours following the ARDSnet strategy (2) and for the subsequent 12 hours following the stress index strategy, or vice versa. The sequence of application of the two strategies was randomly assigned to patients using a concealed allocation approach by choosing between sealed envelopes that contained the individual procedure sequence. The stress index strategy used the same ARDSnet ventilatory pattern, except for the PEEP level, which was titrated to effect—that is, targeting a stress index between 0.9 and 1.1, a normal range identified according to previous investigations (12, 15). If, during the ARDSnet strategy application, the stress index was higher than 1.1, PEEP was decreased to achieve a value between 0.9 and 1.1; if stress index values between 0.9 and 1.1 were measured, no change was made; and if the stress index was lower than 0.9, PEEP was increased. Adjustment of PEEP was suspended if any one of the following conditions ensued: plateau pressure > 30 cm H_2O, $Sa_{O_2} < 88\%$, or hemodynamic instability.

At the end of each 12-hour study period, static elastance (partitioned for respiratory system, chest wall, and lung), quasi-static pressure–volume curves of the respiratory system (low-flow technique), and PEEP-induced alveolar recruitment were measured as previously described (5), blood samples were collected for subsequent cytokine determination, and hemodynamic and gas exchange parameters were recorded.

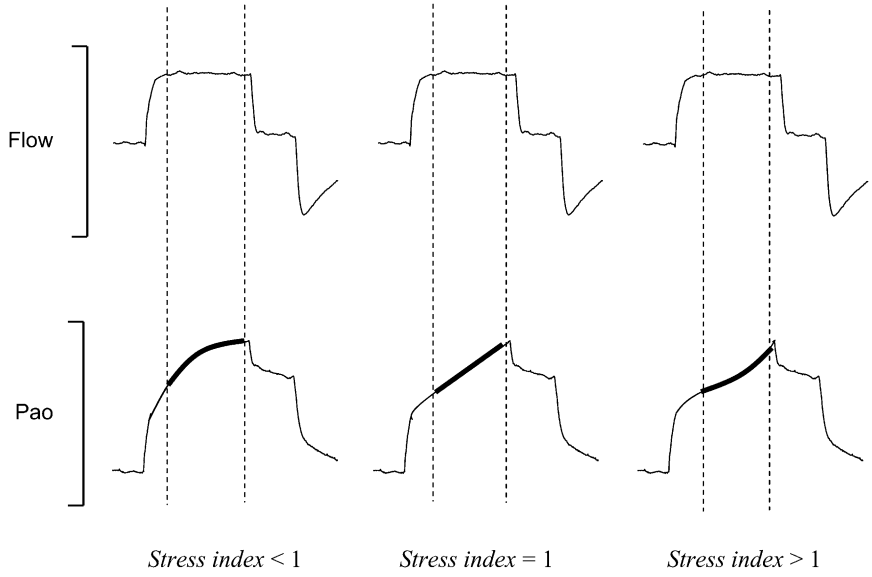

Figure 1. Graphic representation of the stress index concept. The stress index is the coefficient b of a power equation (airway pressure $= a \cdot$ inspiratory time$^b + c$), fitted on the airway opening pressure (Pao) segment (*bold lines*) corresponding to the period of constant-flow inflation (*dotted lines*), during constant-flow, volume-cycled mechanical ventilation. For stress index values of less than 1, the Pao curve presents a downward concavity, suggesting a continuous decrease in elastance during constant-flow inflation. For stress index values higher than 1, the curve presents an upward concavity suggesting a continuous increase in elastance. Finally, for a stress index value equal to 1, the curve is straight, suggesting the absence of tidal variations in elastance.

Statistical Analysis

Data are presented as mean ± SD. Because plasma cytokine determinations were not normally distributed, values were expressed as median and 25th–75th interquartile range. Comparisons between the two ventilatory strategies were performed using analysis of variance for repeated measures followed by a Student *t* test for paired samples, or a Wilcoxon signed-rank test, where appropriate. A P value of less than 0.05 indicated significant differences between values. Statistical analysis was performed using the software package StatView (Abacus, Inc., Berkeley, CA).

RESULTS

The study was conducted in from January 2004 to February 2006. In this period, 964 patients were admitted to our 16-bed intensive care unit. ARDS was diagnosed in 114 (11.8%) of patients. Of those, 92 (80.7%) patients underwent thoracic CT scan within the first 3 days of diagnosis of ARDS, and the qualitative analysis of CT scans according to the CT Scan ARDS study group criteria revealed a focal, patchy, and diffuse pattern of loss of aeration in 30 (32.6%), 44 (47.8%), and 18 (19.6%) of patients, respectively. Hence, only 30 patients with early focal ARDS were considered eligible for inclusion in the study. Of those, 15 were excluded (10 because they did not meet the inclusion criteria of the ARDSnet protocol, 5 because they refused informed consent). All the 15 patients admitted completed the study; of those, 7 were randomized to the sequence ARDSnet strategy–stress index strategy and 8 to the stress index–ARDSnet strategy. Baseline ventilatory settings and demographic and clinical data of the 15 patients enrolled in the study are shown in Table 1. In seven patients, ARDS was of pulmonary origin.

In all patients, the stress index value during ARDSnet strategy ventilation was higher than 1.1 (1.154 ± 0.054). To implement the stress index strategy, in all patients PEEP was reduced accordingly. The target stress index range (0.90–1.1) was reached in all patients (1.008 ± 0.054, $P < 0.01$, vs. the ARDSnet strategy phase of ventilation) (Figure 2). Throughout the stress index strategy ventilation period, the stress index was kept in the target range by adjusting PEEP once every hour (i.e., within the first 5–10 min). A transient (10–15 min) increase in sedation to Ramsay 5 was required in 42 of 210 stress index measurements (20%) to suppress spontaneous inspiratory efforts. Figure 3 displays the airway opening pressure and flow traces under the two experimental conditions in a representative patient.

Figure 2 and Table 2 show the ventilatory, respiratory mechanics, and gas exchange parameters at the end of each study period. By protocol, $F_{I_{O_2}}$ and V_T were left unchanged. The PEEP value was significantly lower during the period the stress index strategy was used as compared with the period the ARDSnet strategy was used (6.8 ± 2.2 vs. 13.2 ± 2.4 cm H_2O, $P < 0.01$). The $Pa_{O_2}/F_{I_{O_2}}$ ratio was not significantly affected by the PEEP reduction. The Pa_{CO_2} was slightly but significantly lower during the stress index as compared with the ARDSnet strategy period, although the minute volume was not significantly different. Static respiratory system and lung elastance were significantly higher during the period of ARDSnet application, whereas static chest wall elastance remained unchanged between the two strategies.

Figure 4 shows the quasi-static volume–pressure curves obtained in three representative patients under the two experimental conditions. Of note, the volume–pressure curves recorded during the ARDSnet strategy application were almost superimposed to those measured during the period the stress index strategy was applied, indicating minimal differences in alveolar derecruitment between the two strategies, despite a significant PEEP reduction. Overall, the alveolar derecruitment was between 25 and 145 ml (mean, 70 ± 39 ml).

Cardiac output was significantly lower (6 ± 0.8 vs. 7.1 ± 1.4 L/min, $P = 0.0163$) and systemic vascular resistances higher (1,190 ± 200 vs. 974 ± 297 dyne · s · cm^{-5}, $P = 0.0491$) when the ARDSnet strategy was applied. Mean arterial pressure and heart rate were not different.

Plasma levels of IL-6, IL-8, and sTNF-α RI were significantly higher during the phase of ARDSnet ventilation than during the period of stress index–guided ventilation, whereas the levels of TNF-α and sTNF-α RII were not significantly affected by the two strategies (Figure 5).

TABLE 1. PATIENT CHARACTERISTICS AND VENTILATORY SETTINGS OF THE ARDSnet STRATEGY AT STUDY ENTRY

Strategy Order*	Age (*yr*)	Sex	APACHE III	Height (*cm*)/ PBW (*kg*)	MV/ARDS† (*d*)	V_T (*ml*)	Backup RR	$F_{I_{O_2}}$	PEEP (*cm H_2O*)	Underlying Disease	Outcome
2	76	M	86	175/70	2/1	420	25	0.7	12	Pancreatitis	D
1	74	F	67	170/61	7/1	380	20	0.5	8	VAP	A
1	38	M	45	202/95	9/2	580	20	0.7	10	VAP	D
2	68	F	55	172/63	1/1	380	15	0.5	10	Abdominal sepsis	A
2	60	M	78	174/70	2/1	420	25	0.7	12	Abdominal sepsis	D
1	74	M	85	175/70	3/3	420	22	0.8	14	Abdominal sepsis	D
2	77	M	45	176/71	3/2	430	20	0.7	12	Pneumonia	A
1	67	F	70	170/61	2/2	380	16	0.8	14	Abdominal sepsis	A
1	80	F	51	160/52	6/2	330	24	0.7	14	VAP	D
2	61	F	72	165/57	3/1	370	15	0.9	16	Sepsis	A
1	47	F	76	172/63	3/3	400	20	0.9	16	Pneumonia	A
2	72	F	100	170/61	2/1	380	29	0.7	14	Polytrauma	A
2	35	F	91	175/66	3/3	420	22	0.9	16	Polytrauma	A
1	55	M	105	180/75	2/1	450	15	0.9	14	Pneumonia	A
2	57	M	86	170/66	3/3	420	15	0.9	16	Pneumonia	D

Definition of abbreviations: A = alive; APACHE = Acute Physiology and Chronic Health Evaluation score (the score can range from 0 to 299, with higher scores indicating a higher probability of death); ARDS = acute respiratory distress syndrome; D = dead; MV = mechanical ventilation; PBW = predicted body weight; PEEP = positive end-expiratory pressure; RR = respiratory rate; VAP = ventilator-associated pneumonia.

* Strategy order: order of application of the two strategies resulting from the randomization procedure: (*1*) ARDSnet–stress index; (*2*) stress index–ARDSnet.

† Days since the diagnosis of ARDS compared with days of MV.

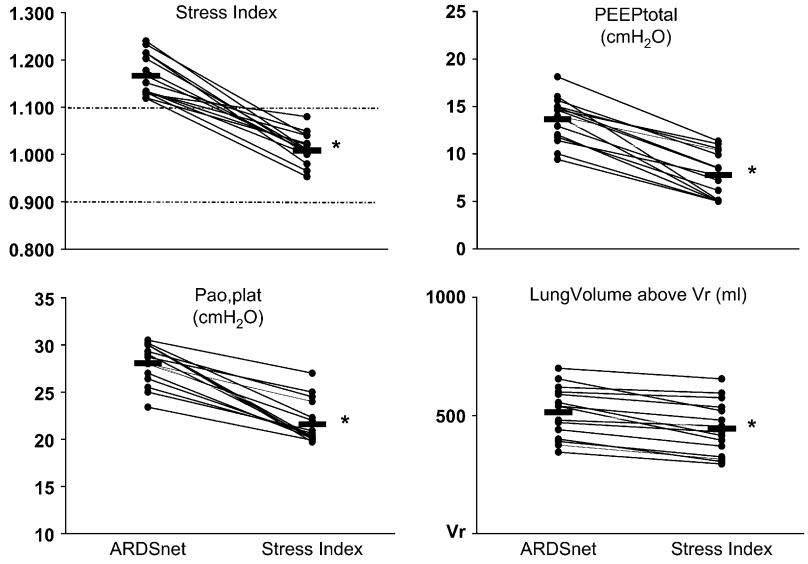

Figure 2. Individual values, recorded at the end of each experimental condition, of stress index, total positive end-expiratory pressure (PEEPtotal) (plateau pressure in airway opening pressure during a 3–5-s end-expiratory occlusion), inspiratory airway opening plateau pressure (Pao, plat [plateau pressure in airway opening pressure during a 3–5-s end-inspiratory occlusion]), and lung volume above the elastic equilibrium volume of the respiratory system (relaxation volume [Vr]), measured on the static pressure–volume curve at a pressure of 20 cm H_2O. For further detail on these measurements, *see* the online supplement. *$P < 0.01$.

DISCUSSION

Our data support the hypothesis that application of the ARDSnet protocol may generate tidal alveolar hyperinflation in patients with ARDS with a focal pattern of loss of aeration. Furthermore, they show that the observed hyperinflation is likely due to the PEEP setting criteria of this specific protocol (table based, alternating PEEP and $F_{I_{O_2}}$ increases to achieve an oxygenation target). We demonstrated that adjusting PEEP based on the respiratory system mechanics of an individual patient allows reduced risk of alveolar hyperinflation.

In the present study, the application of the stress index analysis revealed the occurrence of tidal alveolar hyperinflation in patients with focal ARDS who were ventilated using the ARDSnet protocol. Previous studies have documented the ability of the stress index to qualitatively detect alveolar hyperinflation in humans, both in adults (13) and children (19), as compared with static pressure–volume curves. However, human studies comparing the stress index method against the reference CT scan method are not available. A recent experimental CT study demonstrated that the amount of lung tissue subject to tidal alveolar hyperinflation grows exponentially for stress index values higher than 1.1, whereas it is negligible for stress index vales in the 0.9–1.1 range (15), but we must point out that this study was conducted in a surfactant-depleted ARDS model and under a wide range of stress indices. Therefore, the ability of the stress index to exactly quantify the amount of lung tissue undergoing tidal alveolar hyperinflation in the clinical context needs further validation. Moreover, Pa_{CO_2} was significantly higher during the ARDSnet strategy period, whereas minute ventilation was not significantly different between the two modalities (Table 2). This provides further indirect evidence for alveolar overinflation during ARDSnet strategy–guided ventilation (20), but because we have compared Pa_{CO_2} values recorded at the end of each study period (i.e., at a time interval of 12 h), effects of differences in metabolic CO_2 production therefore cannot be

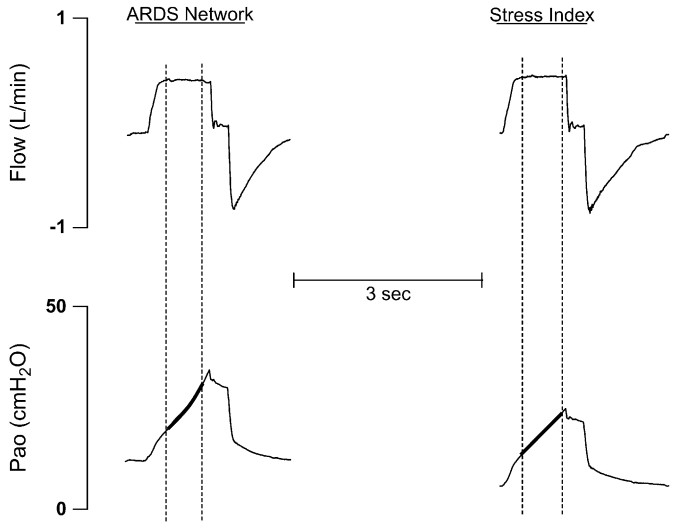

Figure 3. Experimental record showing flow and airway opening pressure (Pao) traces obtained in a representative patient during the two experimental conditions. *Dotted lines* identify the portion of constant-flow inflation and the *bold lines* the corresponding segment of Pao on which the software fits the power equation for the stress index calculation. During the ARDSnet strategy, the stress index value was 1.233, with a positive end-expiratory pressure (PEEP) level of 12 cm H_2O, whereas it was reduced to 1.006 during the stress index strategy, with a PEEP level of 5 cm H_2O.

TABLE 2. VENTILATORY PARAMETERS, PARTITIONED STATIC ELASTANCE, AND GAS EXCHANGE PARAMETERS AT THE END OF EACH STUDY PERIOD

	ARDSnet	Stress Index	*P* Value
$PEEP_{external}$, cm H_2O	13.2 ± 2.4	6.8 ± 2.2	<0.01
$PEEP_{i,st}$, cm H_2O	0.9 ± 1.1	1.1 ± 1.6	NS
V_T, ml	420 ± 80	440 ± 60	NS
RR, breaths/min	23 ± 5	22 ± 4	NS
Minute ventilation, L/min	8.6 ± 2.8	9 ± 3.1	NS
Est_{rs}, cm H_2O/L	34.7 ± 6.6	31.2 ± 7.4	<0.01
Est_L, cm H_2O/L	28.6 ± 6.7	26.3 ± 7.1	<0.01
Est_{cw}, cm H_2O/L	5.9 ± 2.4	6.2 ± 2.4	NS
$F_{I_{O_2}}$	0.75 ± 0.14	0.76 ± 0.13	NS
pH	7.397 ± 0.1	7.408 ± 0.1	NS
$Pa_{O_2}/F_{I_{O_2}}$	122 ± 44	110 ± 32	NS
Pa_{CO_2}, mm Hg	45.6 ± 6.1	41.8 ± 6.3	<0.01

Definition of abbreviations: Est_{cw} = static elastance of chest wall; Est_L = static elastance of lung; Est_{rs} = static elastance of respiratory system; NS = not significant; PEEP = positive end-expiratory pressure; $PEEP_{external}$ = PEEP at end expiration; $PEEP_{i,st}$ = static intrinsic PEEP; RR = respiratory rate.

Data are mean ± SD.

ruled out. Finally, despite the PEEP level being significantly lower during the stress index strategy period as compared with the phase when the ARDSnet strategy was applied, static lung elastance improved and a slight, albeit significant, alveolar derecruitment occurred without worsening of arterial oxygenation. These data indirectly suggest that alveolar hyperinflation had developed during the ARDSnet ventilation period.

The rationale of the ARDSnet protective ventilatory strategy (2) is to minimize tidal alveolar hyperinflation, a well-known cause of ventilator-induced lung injury (1). The practical and standardized approach chosen by the ARDSnet investigators was deemed appropriate for a multicenter clinical study, involving hundreds of patients (21). However, ARDS is a complex condition, characterized by differences in etiology (22), severity, derangement of respiratory mechanics, and potential for alveolar recruitment (6). In patients with focal ARDS, lacking alveolar recruitment, oxygenation is likely more influenced by the applied $F_{I_{O_2}}$ than by PEEP (23), and we may speculate (as recently suggested [24]) that applying the ARDSnet PEEP–$F_{I_{O_2}}$ table (which mandates simultaneous PEEP and $F_{I_{O_2}}$ increases) may lead to the selection of higher PEEP levels merely to arrive at the higher $F_{I_{O_2}}$ levels predicted in the table, which unfortunately provokes tidal alveolar hyperinflation. Our data suggest that, in patients with focal ARDS, titrating PEEP to a lower level than the one prescribed by the ARDSnet protocol allows reducing the risk of hyperinflation and elevated plasma levels of inflammatory mediators. However, this implies that the development of dependent atelectasis is to some extent "tolerated." Another possible approach would be use of aggressive recruitment maneuvers (in which airway pressures would be raised to values as high as 60 cm H_2O) with subsequent use of high PEEP levels. Such a strategy has recently been shown to drastically reduce atelectasis, hyperinflation, and lung inflammation (25). Further studies are warranted to determine whether one of those two opposite approaches would be more beneficial in terms of clinical outcome parameters (3, 24, 26).

In our patients, plateau pressure was lower than 30 cm H_2O during the period when the ARDSnet strategy was applied. Although several studies have suggested that this is a relatively safe threshold, we found a significant decrease in circulating inflammatory mediators by further lowering plateau pressures during the stress index strategy. Our data seem to accord with a recent review by Hager and coworkers (27) suggesting that reducing the "safe threshold" for plateau pressure below 30 cm H_2O could further limit ventilator-induced lung injury. In a recent study (28), Terragni and coworkers identified two groups among patients ventilated with the ARDSnet protocol: one "more" and one "less" protected against lung mechanical stress. Interestingly, less protected patients were characterized by

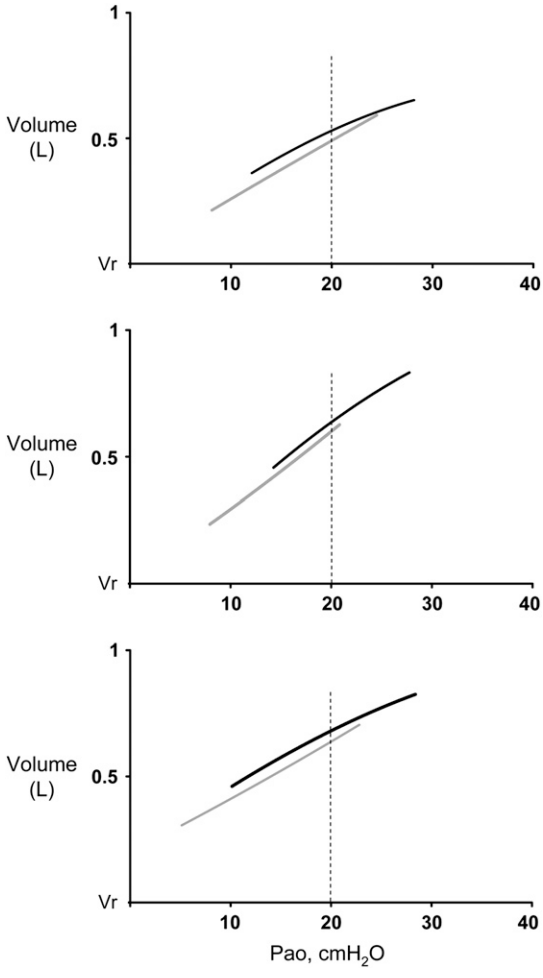

Figure 4. Quasi-static volume–pressure relationship of the respiratory system during low-flow tidal inflation, obtained during the ARDSnet strategy (*solid black lines*) and the stress index strategy (*gray lines*) in three representative patients. Pao = airway opening pressure. The elastic equilibrium volume of the respiratory system (Vr) was used as a reference for both the volume–pressure curves. The volume–pressure curves obtained during the two strategies are almost superimposed, indicating absence of significant difference in positive end-expiratory pressure–induced alveolar recruitment between the two strategies, measured as the difference in lung volume for the same static Pao (20 cm H_2O, *dotted lines*).

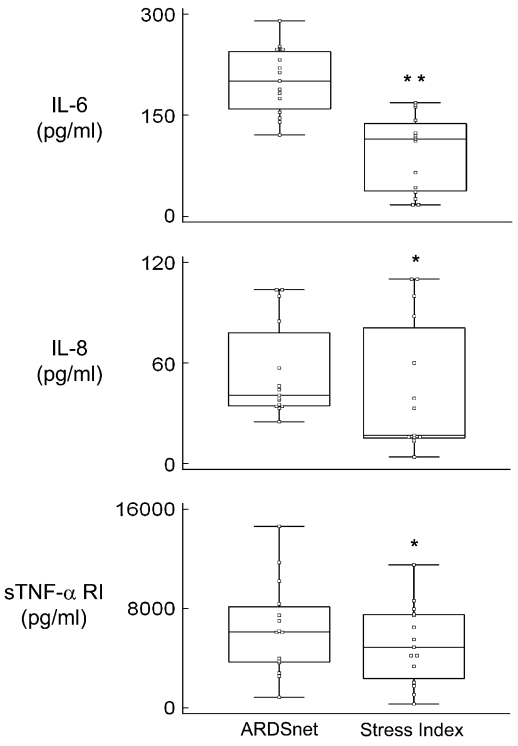

Figure 5. *Box plots* and individual values (*open squares*) showing plasma levels of IL-6, IL-8, and soluble tumor necrosis factor-α receptor I (sTNF-α RI) measured at the end of each study period. *Boxes* show interquartile ranges (25th–75th percentile); the *middle line* indicates the median; the *vertical axis* extends from the minimum to the maximum value. *$P < 0.01$; **$P < 0.05$ (Wilcoxon signed-rank test).

significantly higher plateau pressures when compared with more protected patients. The authors speculated that the V_T limitation prescribed by the ARDSnet protocol could be insufficient in the group of less protected patients. Our data seem to emphasize the role of PEEP in inducing lung hyperinflation in patients with focal ARDS. Of note, the less protected patients in the Terragni study were ventilated with significantly higher PEEP and $F_{I_{O_2}}$ levels than those classified as being more protected, and the authors reported that less protected patients were characterized by a larger, dependent, nonaerated compartment, suggesting that they were affected by focal ARDS.

We have tested a protective ventilatory protocol different from that of the ARDSnet because the PEEP level was chosen on the basis of stress index monitoring. The main advantage of the stress index monitoring is the potential for breath-by-breath determination of ventilator-induced lung mechanical stress, accomplished without the need for disconnecting the patient from the ventilator or changing ventilatory settings. In addition, if lung parenchyma is not homogeneously diseased, it could theoretically happen that regions where resistances and/or compliance are lower are dynamically hyperinflated during tidal inflation (29). None of the pressure–volume curves measured under static or quasi-static conditions or CT scans obtained during an end-inspiratory pause may detect such additional amount of alveolar hyperinflation, whereas the stress index may potentially be suitable to do it (14). However, this assumption has not been demonstrated and deserves further investigation. Although several theoretical assumptions are made when interpreting the stress index determination as a valid parameter (11, 12, 15) (*see* the online supplement for further discussion), the stress index has been shown to provide the same information as the static volume–pressure curve regarding the elastic properties of the respiratory system in both adults (13) and children (19). In a rat model, it predicted a noninjurious ventilatory strategy with a high positive power (12), whereas a stress index–guided ventilatory protocol was successfully applied in a mouse lung transplant model to protect the transplanted lung from ventilator-induced lung injury (11). In our study, for the clinical implementation of the stress index, one important point was to rule out the possible influence of spontaneous inspiratory efforts on the shape of the airway pressure–time curve (30). Although we report that 80% of the measurements were possible at a sedation level of Ramsay score 3–4 and that a transient increase to a level 5 allowed the measurement in the remaining 20% of the measurements, in a recent study even a sedation level of Ramsay 5 allowed obtaining a reliable measurement of a quasi-static volume–pressure curve in only 10 of 19 patients with ARDS (31). A possible explanation for the difference between the two studies could be the different time window ($<$1 s) that is needed for the stress index measurement as compared with that necessary for recording of the quasi-static volume–pressure curve (6 s) (31).

Mechanical ventilation may be an important factor in determining systemic cytokine levels in patients with ARDS. Several human and experimental studies have documented that tidal alveolar hyperinflation and/or opening and collapse may increase plasma levels of cytokines, due to the disruption of the alveolar epithelial–endothelial barrier (32–36). This has been considered a mechanism underlying the development of multiple-system organ dysfunction syndrome in these patients (1, 34). Stuber and coworkers documented a sharp increase in plasma levels of TNF-α, IL-6, IL-10, and IL-1β within 1 hour after switching from a protective to an injurious ventilatory strategy, which was reversed as soon as the protective strategy was resumed (35). These data support our study. During the stress index strategy period, we found a significant decrease in plasma levels of IL-6 and IL-8, two key mediators of ventilator-induced lung injury (32). However, in contrast to the former study, we did not find significant variation in plasma levels of TNF-α. We may speculate that these differences may be explained by the fact that, different from the work of Stuber and colleagues, we compared two protective ventilatory strategies. The significant reduction in plasma levels of sTNF-α RI during the stress index strategy application is of particular interest because this receptor (differently than the type II) is directly released from alveolar epithelial cells and has been shown to be a sensitive marker of ventilator-induced lung injury (37). Furthermore, the plasma levels of this receptor are associated with morbidity and mortality in patients with acute lung injury (37).

Some limitations of this study must addressed:

1. The inclusion of patients with "diffuse" or "patchy" patterns of loss of aeration would have potentially broadened the impact of our investigation, and this issue deserves further investigation.
2. The stress index calculation is presently feasible only during constant-flow ventilation, whereas a decelerating ramp inspiratory flow is frequently applied. In the online supplement, we present a theoretical approach to the application of the stress index software in this condition.
3. We report a slight (albeit significant) alveolar derecruitment, without significant changes in arterial oxygenation, even though PEEP was markedly decreased moving from the ARDSnet to the stress index strategy. This finding, which is quite unusual for patients with early ARDS, may be explained by considering that we studied a particular subgroup of patients with ARDS, characterized by a low potential for alveolar recruitment. This significantly limits the possible implications of our study, which must always refer to this cohort of patients.
4. Our data indicate a greater physiologic benefit of the stress index over the ARDSnet approach, but they do not provide direct evidence regarding its superiority over other possible approaches, such as using a different PEEP–$F_{I_{O_2}}$ scale or setting PEEP at the same low level (5–7 cm H_2O) in all patients with focal ARDS, as suggested by Rouby and coworkers (23).
5. A logical implication of the stress index approach—that is, setting V_T based on its impact on the airway opening pressure profile—was not addressed in our study.

In conclusion, our data emphasize the importance of considering both the distribution of loss of aeration and the physiologic effects of PEEP when ventilating patients with ARDS. We have applied for the first time in the clinical setting the stress index strategy, and our results suggest that it could be a better physiologic approach for setting PEEP than the PEEP–$F_{I_{O_2}}$ table. We must emphasize, however, that our short and tightly controlled physiologic study, conducted on a relatively small number of patients, was not designed to evaluate the impact of the two ventilation strategies on clinically meaningful outcome parameters, and therefore any extrapolation of our results to the clinical situation must be conducted with caution.

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