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Relationship between pressure-volume curve and markers for collagen turn-over in early acute respiratory distress syndrome

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Abstract *Objective:* In acute respiratory distress syndrome, the relationships between changes in the elastic behavior of the respiratory system and biological markers of extra-cellular matrix or surfactant turn-over could give some insights into its pathophysiological determinants. *Design and measurements:* In 17 patients with acute respiratory distress syndrome, we assessed the relationship between chord compliance measured on pressure–volume curves obtained at two levels of positive end-expiratory pressure (0 and 10 cm H_2O) and biological markers of collagen turn-over or surfactant degradation in bronchoalveolar lavage fluid obtained simultaneously in the early phase of the disease (first 4 days). *Main results:* The compliance of the respiratory system obtained from the pressure–volume curves was significantly correlated with markers for collagen turn-over (type III procollagen peptide and matrix metalloproteinase 2) and with markers of surfactant degradation (type-IIA secretory phospholipase A2). The correlations were stronger when the curve was traced from positive end-expiratory pressure, suggesting that this condition may improve the assessment of tissue mechanics. A logarithmic relationship best described the correlation between compliance and type III procollagen peptide, in agreement with a collagen-dependent model of maximal distension. The marker for surfactant degradation was associated with ongoing alveolar inflammation (cellularity of bronchoalveolar lavage fluid and tumor necrosis factor-α concentration). Interleukin-10, an anti-inflammatory mediator, showed no correlation with compliance. *Conclusion:* These preliminary data suggest that a severe reduction in compliance in the early phase of acute respiratory distress syndrome is associated with both collagen deposition and surfactant degradation.

Keywords Type III procollagen peptide · Matrix metalloproteinase-2 · Type-IIA secretory phospholipase A2 · Fibroproliferation · Acute respiratory distress syndrome · Compliance

Introduction

The lungs of patients with acute respiratory distress syndrome (ARDS) are characterized by collagen deposition, as shown by histological analysis [1, 2]. The presence of type III procollagen peptide (*N*-terminal peptide of type III procollagen, PCP III) in bronchoalveolar lavage fluid is correlated with prognosis [1]. Also, proteinases responsible for collagen degradation, such as matrix metalloproteinase 2 (MMP-2), are increased in the bronchoalveolar lavage fluid of these patients and are correlated with markers of extra-cellular matrix degradation [3]. The relationship among these specific features of ARDS lungs and both clinical presentation and physiological derangements has not been well explored.

A decrease in respiratory system compliance is indeed a hallmark of ARDS. Part of this decreased compliance is explained by a reduction in aerated areas (the "baby lung" concept), and whether a decrease in tissue compliance exists remains debatable [4]. Whether markers of collagen deposition could also correlate with changes in compliance, better assessed with the pressure-volume curve, is unknown. Such evidence may be important with regard to the possible administration of anti-fibroproliferative therapy, such as late steroid therapy [5].

The aim of this study was to search for a link between markers of collagen turn-over, namely PCP III and MMP-2 concentrations, in bronchoalveolar lavage fluid, and the compliance of the respiratory system assessed by the pressure–volume curve. Since surfactant degradation/inactivation may also account for the decrease in compliance, the activity of type-IIA secretory phospholipase A2 (sPLA2), an enzyme involved in surfactant degradation [6], was also evaluated. Because the pressure–volume curve at zero end-expiratory pressure (ZEEP) is influenced to a large extent by the ongoing recruitment that takes place during the maneuver itself, we hypothesized that correlations, if any, would be better with measurements taken from the curve from positive end-expiratory pressure (PEEP) [7]. We hypothesized that compliance measurements may be more meaningful after alveolar recruitment. Therefore, we specifically investigated chord compliance (C_{LIN}), i.e., the compliance in the linear part of the pressure–volume curve, with and without PEEP [8].

Materials and methods

Patients

We prospectively evaluated patients who were mechanically ventilated and who met standard criteria for ARDS [9] during a 6-month period in the Henri Mondor Hospital. The protocol was approved by the Ethics Committee of the Société de Réanimation de Langue Française, and informed consent was obtained from each patient's next of kin.

Patients were studied when bronchoalveolar lavage (BAL) was considered necessary by the attending physician, either to evaluate a suspicion of ventilator-associated pneumonia or to screen for colonization and/or infection [10]. Only early investigations (during the first 4 days of the syndrome) were considered for this study. Non-inclusion criteria were a documented history of chronic obstructive or interstitial pulmonary disease, a contraindication for neuromuscular blockade, a PaO_2 / FiO_2 ratio less than 80 mmHg, severe hemodynamic instability, an endotracheal tube inner diameter less than 7 mm, and presence of a chest tube with air leaks. None of the patients received high-dose corticosteroid treatment at the time of assessment. All patients were ventilated with a 6 ml/kg of estimated body weight. PEEP was titrated individually according to oxygenation, hemodynamics, and plateau pressure. Plateau pressure was kept at 30 cm H_2O or below.

Recording of the elastic pressure–volume curve of the respiratory system

The system, including a computer-controlled Servo Ventilator 900C, and the technique for recording pressure–volume curves based on the oscillating flow insufflation method have been described in detail elsewhere [7, 8, 11]. Pressure–volume curves were obtained at 10 cm H_2O of PEEP, then at ZEEP. Chord compliance (C_{LIN}) was defined as the slope of the linear part of the pressure–volume curve. PEEP-related recruitment was defined, for a given elastic pressure, as the volume difference between the two curves, taking intrinsic PEEP into account, as described elsewhere [8].

Bronchoalveolar lavage fluid collection

Bronchoalveolar lavage fluid collection (BAL) was performed within 24 h of the pressure–volume curve study. Total and differential cell counts were obtained from a BAL fluid aliquot. BAL was separated into its acellular and cellular components by centrifugation at 300×g for 7 min, and supernatants were frozen at –80°C until use, as described elsewhere [12].

Assays

Type III procollagen peptide (*N*-terminal peptide of type III procollagen, PCP III) was measured using a radioimmunoassay (RIA-gnost P III P; CIS Bio International, Gif sur Yvette, France). Type-IIA secretory phospholipase A2 (sPLA2) was measured using a fluorometric assay

shown to be selective for secretory PLA2, as previously described [6, 13]. To establish that the enzyme assayed was the sPLA2-IIA form, we used the sPLA2-IIA activity inhibitor LY311727, which almost completely abolished the PLA2 activity detected in BAL fluids. Type 2 matrix metalloproteinase (total MMP-2, gelatinase A), tumor necrosis factor-α and interleukin-10 were evaluated using ELISAs according to the manufacturer's instructions (R&D Systems, Lille, France). All mediator concentrations are expressed per ml of recuperated BAL fluid; their minimum detectable concentrations were 0.16 ng/ml, 1.6 pg/ml, and 3.9 pg/ml respectively.

Statistical analysis

All data are expressed as medians (25th to 75th percentiles). Data were analyzed using Statview 5.0 (SAS Institute, Cary, NC, USA). For intergroup comparisons, continuous variables were compared using the Mann-Whitney U test. For intragroup comparisons, continuous variables were compared using the Wilcoxon paired test. The Spearman's rank correlation coefficient was used to examine possible correlation between two variables, except when stated otherwise. *P* values less than 0.05 were considered statistically significant. The problem of functional relevance depends on the context. Inasmuch as compliance impairment during ARDS probably relies on several parameters, all significant associations are reported when justified by background knowledge even if causation cannot be directly inferred. On the other hand, since this study was conducted on a limited number of patients, we deliberately decided not to show the negative results, which lack the statistical power to rule out a possible correlation.

Results

Patients

We included 17 patients (13 men, 4 women) whose characteristics are described in Table 1. ARDS was related to direct lung injury in 15 patients and indirect injury in 2 patients. Only 4 out of 17 BAL fluids showed significant bacterial growth ($\geq 10^4$ colony-forming units/ml) indicating the presence of bacterial superinfection, while 6 BAL fluids showed non-significant bacterial growth (colonization) and 7 fluids were sterile.

Respiratory mechanics

Individual values for respiratory mechanics are provided in Table 1. The median $C_{LIN,ZEEP}$ was significantly higher than the median $C_{LIN,PEEP}$ ($P = 0.0004$, Wilcoxon test). The relationship between PEEP-induced alveolar recruitment and $C_{LIN,PEEP}$ was close to significance (Spearman's Rho = 0.47, $P = 0.05$).

Relationships between BAL mediators and respiratory system mechanics

Median concentrations of PCP III and MMP-2 were 0.13 U/ml (0.04–2.27) and 7 ng/ml (2–18) respectively, which were highly correlated (Fig. 1). We found significant correlations between chord compliance and markers for collagen turn-over, i.e., PCP III and MMP-2 (Fig. 1). These correlations were not linear, but instead tended to describe a logarithmic shape, a model already described in the literature for collagen-dependent maximum distension of the fibrous skeleton of the lungs (see the level of statistical significance using logarithmic regression analysis in Fig. 1). The associations between these indexes of collagen turn-over and respiratory mechanics were stronger when compliance was measured with PEEP compared with ZEEP (in ZEEP: PCP III, $R^2 = 0.25$; MMP-2, $R^2 = 0.24$; in PEEP: see Fig. 1). These markers for collagen turn-over were also correlated with the degree of PEEP-induced alveolar recruitment as measured from the pressure–volume curves (MMP-2: Rho = –0.50, $P = 0.044$; PCP III: Rho = –0.62, $P = 0.013$).

The median number of inflammatory cells in BAL fluid was 308,000/ml (151,500–967,500) with a median of 76% neutrophils (38–87). Median sPLA2 activity was 77 U/ml (21–736) and median tumor necrosis factor-α concentration was 14 pg/ml (0–45). A significant correlation was found between chord compliance and sPLA2 activity in BAL fluid ($C_{LIN,PEEP}$, Rho = –0.59, $P = 0.023$). Activity of sPLA2 was significantly associated with markers for alveolar inflammation; namely, the alveolar neutrophil count (Rho = 0.65, $P = 0.021$) and the tumor necrosis factor-α concentration (Rho = 0.62, $P = 0.018$). The interleukin-10 level (median 1.8 pg/ml [0.2–10.8]) was not significantly correlated with any of the BAL fluid parameters or with the pressure–volume curve assessment.

Determination of a cut-off value of $C_{LIN,PEEP}$ with functional consequences

The functional consequences of a cut-off value of $C_{LIN,PEEP}$ were examined. From the regression equation we calculated the value of $C_{LIN,PEEP}$ corresponding to a concentration of 1.75 U/ml of PCP III, which has been demonstrated to have prognostic significance, and because below this value the parameters of collagen turn-over depicted a plateau [14]. The cut-off value of 1.75 U/ml corresponds to a value of chord compliance equal to 28 ml/cm H_2O. PCP III levels, MMP-2 levels, and sPLA2 activity were indeed very different for patients

Table 1 Characteristics of the 17 patients. P–F ratio of arterial oxygen tension over fraction of inspired oxygen, SAPS II Simplified Acute Physiologic Score, MV mechanical ventilation, Cp chord compliance; ZEEP zero end-expiratory pressure, PEEP positive end-expiratory pressure, BALF bronchoalveolar lavage fluid culture, MRSA methicillin-resistant *S. aureus*, GP other gram-positive organisms, GN gram-negative organisms, TEN toxic epidermal necrolysis

								Early evaluation					
Case	Sex	Age (years)	Cause of ARDS	Initial P–F ratio (mmHg)	SAPS II value	MV duration (days)	Outcome	Day [c]	BALF culture	Cp ZEEP (ml/cm H_2O)	Cp PEEP (ml/cm H_2O)	Volume recruited at 15 cm H_2O (ml)	P–F ratio (mmHg)
1	Male	37	Endocarditis	87	24	5	Survived	1	Sterile	36	30	182	167
2	Female	55	Pneumonia	162	33	14	Died	3	MRSA-GN [a]	81	60	256	205
3	Male	68	Septic shock	127	46	4	Died	2	Sterile	49	29	218	146
4	Male	52	Aspiration	74	50	15	Survived	4	MRSA [a]	53	38	184	215
5	Male	54	Pneumonia	176	47	3	Died	2	GN [b]	36	26	67	85
6	Male	74	Pneumonia	198	39	7	Died	4	MRSA-GN [b]	28	18	131	85
7	Male	62	Pneumonia	57	73	34	Died	3	GN [a]	42	23	218	86
8	Male	46	Pneumonia	65	58	8	Survived	3	GN [a]	57	39	274	166
9	Male	77	Aspiration	114	71	10	Died	2	Sterile	93	56	240	80
10	Male	65	Aspiration	57	94	6	Died	1	GP [a]	78	64	214	95
11	Male	32	Aspiration	150	37	6	Survived	4	GN [b]	95	49	127	198
12	Female	46	Aspiration	198	36	23	Survived	2	Sterile	39	21	186	84
13	Male	68	Pneumonia	106	39	23	Died	4	Sterile	36	23	238	80
14	Male	46	Aspiration	61	76	8	Died	2	GN [a]	63	48	247	178
15	Female	74	Aspiration	128	61	11	Died	1	Sterile	33	21	106	170
16	Female	18	TEN	136	46	9	Died	2	Sterile	53	37	222	158
17	Male	71	Aspiration	160	26	37	Died	1	GN [b]	40	41	291	106
Median		55		127	46	9				49	37	218	146
percentiles (25th–75th)		(46–69)		(72–160)	(37–63)	(6–17)				(36–67)	(23–48)	(169–242)	(85–172)

[a] Colonization (BALF culture $< 10^4$ cfu/ml)
[b] Infection (BALF culture $\geq 10^4$ cfu/ml)
[c] Days from ARDS onset to assessment

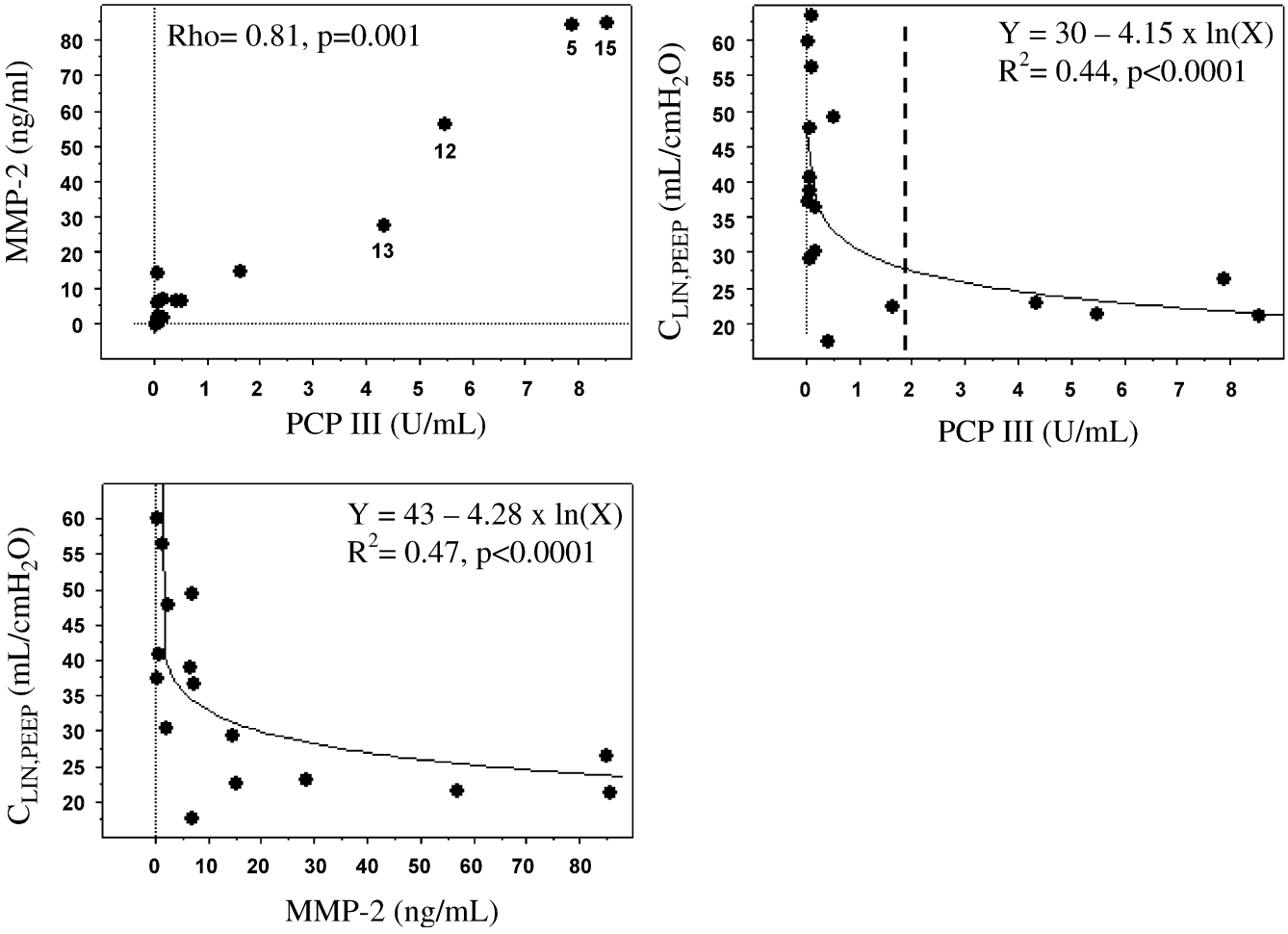

Fig. 1 Correlations between markers for collagen turn-over and chord compliance measured using 10 cm H_2O of PEEP ($C_{LIN,PEEP}$). *Top left panel:* a close correlation exists between levels of the two markers for collagen turn-over, type III procollagen peptide (PCP III), and type 2 matrix metalloproteinase (MMP-2), in bronchoalveolar lavage fluid. The case numbers of the 4 patients with the highest concentrations of the mediators are indicated for information. Their tumor necrosis factor-α concentrations were: 74.6 (case 5), 7.9 (12), < 1.6 (13), and 214.6 (15) pg/ml. *Top right panel:* PCP III level in bronchoalveolar lavage fluid is correlated with $C_{LIN,PEEP}$ (Rho = −0.64, $P = 0.010$). The logarithmic shape of the curve is consistent with the model of collagen-dependent maximal distension (the equation of the logarithmic transformation and the P value are given in the figure). The vertical dashed line indicates a PCP III concentration of 1.75 U/ml, a cut-off reported by Clark and colleagues to be associated with outcome [14]. *Bottom panel:* MMP-2 concentration in bronchoalveolar lavage fluid is correlated with $C_{LIN,PEEP}$ (Rho = −0.74, $P = 0.003$). As with PCP III, the logarithmic curve is shown (the equation of the logarithmic transformation and the P value are given in the figure)

with a $C_{LIN,PEEP}$ below or above 28 ml/cm H_2O. The results are shown in Table 2.

Discussion

The main results of this study conducted in a selected group of patients with early ARDS are the following: respiratory compliance impairment was correlated with biological markers for collagen turn-over (PCP III, MMP-2) and with an indirect index of surfactant degradation (sPLA2 activity) as previously suggested in an animal study [15]. This latter parameter was correlated with alveolar tumor necrosis factor-α concentration and neutrophil counts, indicating a link with an ongoing pro-inflammatory process in the alveolar spaces. No correlation was found with an anti-inflammatory marker. The observed cytokine concentrations are of similar magnitude than those previously published [16].

To our knowledge, this is the first study comparing respiratory mechanics and biological markers for increased alveolar instability (surfactant degradation) and collagen turn-over (PCP III and MMP-2) in patients with ARDS. The results of this study could be considered as preliminary and need to be interpreted cautiously. First, discussion of some methodological limitations warrants discus-

Table 2 Functional relevance of a cut-off value of $C_{LIN,PEEP}$. The calculated value of corresponding to a concentration of PCP III of 1.75 U/ml is 27.7 ml/cm H_2O. SAPS II Simplified Acute Physiologic Score, $C_{LIN,PEEP}$ chord compliance under positive end-expiratory pressure, TNF tumor necrosis factor, BAL bronchoalveolar lavage

Parameter	$C_{LIN,PEEP} \geq 28$ ml/cm H_2O ($n = 11$)		$C_{LIN,PEEP} < 28$ ml/cm H_2O ($n = 6$)		*P* value
P–F ratio (mmHg)	166	(116–193)	85	(84–86)	0.030
Volume recruited (ml)	222	(191–254)	159	(106–218)	0.057
PCP III (U/ml)	0.05	(0.03–0.13)	4.9	(1.6–7.9)	0.001
MMP-2 (ng/ml)	2.19	(0.37–6.7)	42.5	(14.6–84.9)	0.002
sPLA2 activity (U/ml)	23	(21–124)	736	(103–1608)	0.002
TNF-α (pg/ml)	2	(0–31)	26	(8–75)	0.24
Total BAL cell count $10^3(ml^{-1})$	250	(131–452)	1,060	(252–1,294)	0.079
SAPS II	46	(34–68)	43	(39–61)	0.92

sion. BAL was carried out early in the course of ARDS, as part of the initial bacteriological work-up. Some of the results could have explained by infection rather than inflammation. Whether the biological response evidenced univocally reflected the inflammatory response due to ARDS and/or due to bacterial infection or colonization is a complex issue inasmuch as cytokines may promote bacterial growth per se [17]. Median values of the different parameters (except the percentage of neutrophils in BAL fluid), however, were similar when comparing patients with pneumonia at admission or at the time of BAL with other non-infected patients (see electronic supplementary material). We studied relatively early ARDS, since a rapid onset of fibroproliferation has already been suggested by both animal and human studies [18, 19, 20, 21], but this precludes us from extrapolating our results to different stages of the disease.

PCP III is a collagen precursor that reflects collagen deposition, as reported by Farjanel et al., who showed a relationship between PCP III levels and histological fibrosis severity in patients with ARDS [1]. Elevated PCP III levels have been found in ARDS pulmonary edema fluid and in BAL fluid from patients with ARDS as early as 24 h after injury [19, 20]. Both histological fibrosis and PCP III levels in BAL fluid are correlated with the outcome of ARDS [2, 5, 14, 18]. MMP-2 is a metalloproteinase mainly produced by non-inflammatory cells and is responsible for collagen degradation. We have previously shown that the activated form of MMP-2 is increased in BAL fluid from ARDS patients [12]. Torii and co-authors reported a relationship between MMP-2 concentrations and markers for matrix degradation (concentrations of the 7S portion of type IV collagen and laminin) in BAL fluid from ARDS patients [3]. Our data further support this relationship by showing a strong correlation between MMP-2 and PCP III concentrations. This human study also confirms animal data demonstrating that extracellular matrix deposition reflected by markers of collagen turn-over occurs early in the course of acute lung injury [21, 22].

The fall in respiratory system compliance associated with lung injury is considered to reflect more the magnitude of lung volume reduction than the severity of diffuse damage to the entire lung. Nevertheless, recent studies have established that lung areas with a normal appearance on plain radiographs show increased density on computed tomography images, indicating that lung tissue alterations are diffuse in patients with ARDS [23]. Therefore, a weak but significant correlation of biological markers for collagen turn-over and the reduction in compliance may be expected. It could be hypothesized that this relationship might be improved by adjusting for the fall in absolute lung volume. This hypothesis may warrant further investigation.

Although the correlations between compliance and markers for collagen turn-over in our study may seem weak, their logarithmic pattern is consistent with the so-called classical model of collagen-dependent maximal distension [24]. This model reflects the mechanical characteristics of elastin and collagen from freshly excised peripheral pulmonary parenchyma [24]. It suggests that until collagen deposition reaches a threshold level, reflected in our study by a PCP III concentration above 1.75 U/ml, chord compliance is not or is little influenced by collagen turn-over (the chord compliance is probably mainly related to elastin content [24]). Up till 30 ml/cm H_2O, reduction in chord compliance is therefore likely to be a result of a lung volume reduction. Above such a value of collagen deposition, compliance may be limited by collagen deposition, which is called at the cellular level the "collagen-dependent maximal distension." The anatomical units of the fibrous skeleton of the lung can be modeled as they are made of extensible elastin and inextensible collagen, which are "folded" in the lung resting position. The limits of distension are dictated by the inextensible collagen fibers, which work as a "stop length" system. When the collagen fibers are fully unfolded, the lungs reach their maximal volume and further elongation is prevented. Our results may in part reflect at the respiratory system level the results obtained by Rocco and colleagues in an animal model of paraquat-induced acute lung injury [21]. In their animal study, elastance first showed a sigmoidal increase as the amount of collagen increased, but subsequently reached

a plateau [21]. Interestingly, changes in the mechanical behavior of lung tissue occurred early, within 24 h of injury, even in mildly abnormal lung parenchyma [21].

An increase in sPLA2 activity has been demonstrated in BAL fluid from ARDS patients [25]. In an experimental study in rats, we found that sPLA2 activity was involved in surfactant degradation and was associated with a greater reduction in respiratory system compliance [6]. In this animal study, increased sPLA2 activity was also correlated with alveolar inflammation, in keeping with the data from our present study in humans.

The significant correlation linking compliance to biological markers in the present study suggest that compliance might be indirectly affected by alveolar remodeling, even in the early phase of ARDS. Measurements obtained from ZEEP are obscured by the part of collapsed lung that is reopened during recording of the pressure–volume curve itself [7]. Recruitment by PEEP was associated with a further decrease in compliance; as previously shown [8], PEEP can improve ventilation homogeneity via alveolar recruitment, and compliance measurements obtained with PEEP ($C_{LIN,PEEP}$) may therefore better reflect the alterations in lung tissue mechanics, as recruitable lung areas are already reopened. When the lung has been reopened with PEEP, the additional recruitment that takes place during the maneuver is minimized, so that the assessment of mechanics may better reflect the severity of lung injury, yielding closer correlations with biological abnormalities. In keeping with this hypothesis, the two markers for collagen turn-over measured in our study, i.e., PCP III and MMP-2, were more closely correlated with $C_{LIN,PEEP}$ than with $C_{LIN,ZEEP}$, and higher PCP III and MMP-2 levels were associated with less lung recruitment. This latter result traduces that higher levels of PCP III and MMP-2 are associated with less recruitable alveoli and more profound alterations of tissue mechanics.

One consequence of these preliminary results may be to suggest that when chord compliance value is severely impaired (here below 28 ml/cm H_2O), the reduction in compliance may be associated with an intense ongoing fibroproliferative and inflammatory process characterized by inextensible collagen fiber deposition (see Table 2). Along these lines, the recent results of the Late Steroid Rescue Study of the NIH-sponsored ARDSnet further emphasizes the need for early clinical parameters of ongoing fibrosis during ARDS. A post hoc analysis suggested that only patients with the highest levels of PCP III in BAL benefited from steroid rescue therapy in terms of survival (see www.ardsnet.org). Further studies are warranted to confirm our findings, since such a cut-off value could guide the administration of therapies such as steroid administration.

In summary, this preliminary study suggests that respiratory system compliance may be influenced by collagen turn-over and surfactant degradation. These associations occur rapidly in the course of the disease, suggesting early onset of functional consequences of the fibroproliferative process in human beings, which may have future therapeutic consequences.

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