

Lung and chest wall mechanics in patients with acquired immunodeficiency syndrome and severe *Pneumocystis carinii* pneumonia

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Lung and chest wall mechanics in patients with acquired immunodeficiency syndrome and severe Pneumocystis carinii pneumonia. E. D'Angelo, E. Calderini, F.M. Robatto, P. Puccio, J. Milic-Emili. ©ERS Journals Ltd 1997.

ABSTRACT: The aim of this study was to assess the mechanical characteristics of the respiratory system in patients with acquired immune deficiency syndrome (AIDS) and acute respiratory distress syndrome (ARDS) caused by *Pneumocystis carinii* pneumonia (PCP).

In 12 mechanically ventilated patients, total respiratory system mechanics was assessed using the technique of rapid airway occlusion during constant flow inflation, and was partitioned into lung and chest wall components using the oesophageal balloon technique. We measured interrupter resistance (R_{int}), which mainly reflects airway resistance, additional resistance (ΔR) due to viscoelastic behaviour and time constant inequalities, and static elastance (E_{st}). In addition, the static inflation volume-pressure (V - P) curve was assessed. In eight patients, computed tomography scans were performed within 2 days of the assessment of respiratory mechanics.

Compared to values reported in the literature for normal subjects, E_{st} and ΔR were markedly increased in AIDS patients with PCP, whilst R_{int} exhibited a relatively smaller increase. These changes, which involved only the lung and airways, were mainly due to the reduction of ventilated lung units, but additional factors were involved to cause independent modifications of lung stiffness, airway calibre, and viscoelastic properties. The changes in R_{int} , ΔR , and E_{st} were similar to those observed in other studies on patients with ARDS of different aetiologies. At variance with common observations in the latter patients, none of the AIDS patients with PCP exhibited an inflection point on the static inflation V - P curve, suggesting little or no alveolar recruitment during lung inflation.

This finding could be related to the distinctive histopathology of *Pneumocystis carinii* pneumonia. Indeed, computed tomography revealed homogeneous diffuse interstitial and alveolar infiltration rather than the dense, dependent opacities observed in other studies on acute respiratory distress syndrome of different aetiologies.

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Pneumocystis carinii pneumonia (PCP) is the most frequent severe opportunistic infection in patients with acquired immunodeficiency syndrome (AIDS). It is held responsible for up to 85% of episodes of acute respiratory failure that occur in AIDS [1] and 80% of emergency admissions to intensive care units [2, 3], with a reported mortality rate of 75–100% for patients requiring mechanical ventilation [4]. In a recent consensus conference [5], PCP was included, though not by unanimous decision, among the causes of acute respiratory distress syndrome (ARDS), once the following criteria are met: acute onset; arterial oxygen tension (P_{a,O_2})/inspiratory oxygen fraction (F_{I,O_2}) <27 kPa (200 mmHg); bilateral infiltrates on chest radiographs; and no evidence of left atrial hypertension.

ARDS is characterized by increased microvascular permeability leading to a progressive and widespread accumulation of extravascular water in the lung, associated with inflammatory interstitial infiltration and

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marked thickening of the alveolar septa [6, 7]. On the other hand, PCP has a distinctive histopathology: the alveoli are filled with few inflammatory cells and an acellular, eosinophilic, proteinaceous material that contains cysts and trophozoites of the organism, whilst the interstitial spaces contain predominantly mononuclear inflammatory cells [8, 9]. Presence of fibrosis has also been observed, particularly in severe pneumocystosis [10]. This could lead to peculiar changes in the mechanical properties of the respiratory system.

To our knowledge, no systematic study has been performed on the mechanical properties of the respiratory system of patients with AIDS and PCP requiring artificial ventilation. The aim of this study was, therefore, to assess the mechanical characteristics of the respiratory system and its components in such patients in whom ARDS is due to direct lung injury, and compare the results with those reported in the literature for patients with ARDS due to other causes.

Materials and methods

Subjects

Twelve patients (six males) with AIDS (group IV, subgroup C, according to Centers for Disease Control [11]) admitted to the intensive care unit of the San Raffaele Hospital for management of acute respiratory failure due to *P. carinii* pneumonia were studied. Their mean (\pm SD) age, weight and height were 38 ± 8 yrs, 54 ± 8 kg and 166 ± 9 cm, respectively; pertinent clinical data are given in table 1. The diagnosis of PCP was obtained bronchoscopically, and *P. carinii* considered the most important pathogen. The patients were treated for PCP with thrimetoprim-sulphamethoxazole ($20\text{--}100$ mg·kg⁻¹), or pentamidine isethionate (4 mg·kg⁻¹), or trimetrexate (45 mg·kg⁻¹) given intravenously, together with systemic corticosteroids (methylprednisolone, 1.8 mg·kg⁻¹ for 3 days, then gradually reduced). The conventional criteria for ARDS were met in all cases (table 1).

All patients were sedated (thiopental sodium; 2 mg·kg⁻¹·h⁻¹) and paralysed (pancuronium bromide; 2 mg·kg⁻¹·h⁻¹), on the decision of the primary physician. They were nasotracheally intubated with a cuffed endotracheal tube (Mallinckrodt Medical, Athlow, Ireland; $7\text{--}8.5$ mm internal diameter, $30\text{--}36$ cm long) and mechanically ventilated (Siemens Servo Ventilator 900C; Berlin, Germany) in the semirecumbent position. The investigation was approved by the Institutional Ethics Committee and informed consent was obtained from the patients (prior to sedation) or their next of kin. During the study, a physician unconnected with the experimental protocols was always present to provide patient care.

Procedures

The ventilator settings (on intermittent mandatory ventilation (IMV) mode) consisted of a fixed tidal vol-

ume (V_T) (0.43 ± 0.07 L), a fixed inspiratory flow (0.53 ± 0.07 L·s⁻¹), and a respiratory frequency of 14 breaths·min⁻¹. A short (0.4 s) end-inspiratory pause was automatically induced on a breath-by-breath basis by the ventilator, while longer (5 s) end-inspiratory pauses were intermittently ($3\text{--}4$ times) produced by pressing the end-inspiratory hold button. The transistor-transistor logic signal of the ventilator operated a normally open solenoid valve, which was placed in the breathing circuit between the Y-connector and the pneumotachograph. The closing time of the valve ranged $10\text{--}15$ ms depending on the peak pressure in the inspiratory line. The equipment dead space (not including the endotracheal tube) was 150 mL. Special care was taken to avoid air leaks around the tracheal cuff and from the breathing circuit. A single length of standard low-compliance adult tubing (2 cm internal diameter, 110 cm long) was used to minimize errors in mechanics measurements.

Four patients were studied at zero end-expiratory pressure (ZEEP), whilst positive end-expiratory pressure (PEEP; 4.9 ± 1.1 cmH₂O) was applied to the other patients. Changes in end-expiratory lung volume due to PEEP were measured by removing the Y-piece of the ventilator from the pneumotachograph and allowing the patient to exhale until flow ceased. Intrinsic PEEP was not present, as flow became nil at end-expiration and no changes in tracheal pressure (P_{Tr}) occurred on performing end-expiratory airway occlusions.

In order to assess the expiratory reserve volume (ERV) and the vital capacity (VC), the patients were temporarily connected *via* the pneumotachograph to a large syringe (2.5 L). Starting from end-expiratory lung volume, a gentle aspiration was first performed until P_{Tr} became stable in the range $-15\text{--}-25$ cmH₂O, and then the lungs were inflated until P_{Tr} plateaued at values ranging $40\text{--}45$ cmH₂O.

P_{Tr} was measured *via* an end-sealed, noncompliant, polyethylene catheter connected to a pressure transducer (1290A; Hewlett Packard, Andover, MA, USA). The catheter (1.5 mm internal diameter, 50 cm long) had a sealed end and multiple holes in the distal 3 cm and

Table 1. – Clinical characteristics of study population at enrolment

Patient No.	Transmission factor	PCP episode	Other organism in BAL	Intubation days	LIS	$P_{a,O_2}/F_{I,O_2}$ mmHg	P_{a,CO_2} mmHg	Arterial pH	LDH U·L ⁻¹
1	Homo	1st	<i>M. pneumoniae</i>	2	3.0	84	50	7.32	763
2	IVDA	1st		3	2.6	68	49	7.30	2524
3	IVDA	1st	<i>P. aeruginosa</i>	11	2.7	132	46	7.35	1808
4	IVDA	1st	<i>C. alba</i>	9	3.3	75	52	7.26	1161
5	Homo	2nd	<i>S. epidermis</i>	1	2.3	99	55	7.35	1397
6	Hetero	2nd	<i>P. aeruginosa</i>	1	2.8	78	32	7.44	677
7	IVDA	1st		1	2.3	138	34	7.40	1625
8	Hetero	1st		4	2.5	172	50	7.21	1305
9	IVDA	1st	<i>S. aureus</i>	4	2.3	67	47	7.30	1973
10	IVDA	1st		3	2.3	70	37	7.32	1738
11	Hetero	1st	CMV	1	2.7	58	33	7.36	1515
12	Homo	1st		2	3.0	87	31	7.56	900
Mean				3.5	2.7	94	43	7.35	1449
SD				3.4	0.3	35	9	0.09	535

PCP: *Pneumocystis carinii* pneumonia; BAL: bronchoalveolar lavage; P_{a,O_2} : arterial oxygen tension; F_{I,O_2} : inspiratory oxygen fraction; P_{a,CO_2} : arterial carbon dioxide tension; LDH: lactate dehydrogenase; LIS: lung injury score according to MURRAY *et al.* [1]. Homo: homosexual; Hetero: heterosexual; IVDA: intravenous drug abuser; *M.*: Mycoplasma; *P.*: Pseudomonas; *C.*: Candida; *S.*: Staphylococcus; CMV: cytomegalovirus. 1 mmHg = 0.133 kPa.

protruded ~4 cm from the endotracheal tube into the trachea. Oesophageal pressure (P_{oes}) was measured with a similar transducer connected to a thin-walled latex balloon (8 cm long), filled with 0.5–1.0 mL of air through a polyethylene catheter (2 mm internal diameter, 110 cm long), with multiple holes over the balloon length. With this system, pressure measurements were not affected by phase shift or alteration in amplitude up to 20 Hz. Flow (V') was measured with a heated pneumotachograph (Fleisch No. 2; Lausanne, Switzerland) connected to the breathing circuit *via* a cone, and to a differential pressure transducer (Validyne MP-45, ± 2 cmH₂O; Northridge, CA, USA). The response of the pneumotachograph, which was calibrated with the experimental gas mixture, was linear over the experimental range of flows. All signals were recorded on a four-channel pen recorder (7754B; Hewlett-Packard, Cupertino, CA, USA) at a paper speed of 10 mm·s⁻¹. Moreover, they were sampled at 200 Hz by a 12-bit analogue-to-digital converter and stored on a personal computer for subsequent data analysis. Changes in lung volume were then obtained by numerical integration of the flow signal.

The arterial oxygen and carbon dioxide tension (P_{a,CO_2}) and pH (pHa) were measured with a blood gas analyser (IL BG3; Instrumentation Laboratories, Lexington, MA, USA). The electrocardiogram, cardiac frequency, systemic arterial pressure, arterial oxygen saturation (S_{a,O_2}), and end-tidal carbon dioxide tension were continuously monitored (Merlino 56S; Hewlett-Packard, Cupertino, CA, USA). These parameters remained nearly constant throughout the experimental session.

In eight patients, thoracic computed tomography (CT) scans were performed within 2 days of the experimental recordings. A Siemens Somatom CR scanner (Siemens Elema AB, Berlin, Germany) was employed; 20–30 exposures, depending on patient size, were taken at 150 kV, 50 mA, and 5 s.

Data analysis

Respiratory mechanics were assessed by means of the constant flow rapid airway occlusion method [12, 13]. Briefly, end-inspiratory airway occlusions were followed by a rapid initial drop in P_{tr} and P_{oes} (maximal pressure (P_{max}) - pressure at airway occlusion (P_1)) and, during the long-lasting occlusions, by a slow decay to an apparent plateau value. These plateau pressures, computed as the mean of the values recorded between 3.3 and 3.7 s after the occlusion, were taken to represent the static end-inspiratory elastic recoil pressure of the respiratory system ($P_{rs,st}$) and chest wall ($P_{w,st}$), respectively. The rapid pressure drop in P_{oes} became evident only after 30–35 breaths were averaged [14]; to this end, the signals of the individual breaths were superimposed at the onset of airway occlusion as detected on the flow trace. Both P_{tr} and P_{oes} showed some oscillations after airway occlusion; these were allowed for by fitting a smooth curve to the pre- and post-occlusion portions of the pressure signal and by extrapolating the fitted curves to the point in time at which the valve was half-closed to obtain P_{max} and P_1 , respectively. The rapid pressure drops in P_{tr} and P_{oes} divided by the flow preceding the occlusion yield the interrupter

resistance of the respiratory system ($\Delta R_{int,rs}$) and chest wall ($\Delta R_{int,w}$), respectively. The slow pressure drops in P_{tr} and P_{oes} divided by the flow preceding the occlusion yield the additional interrupter resistance of the respiratory system ($R_{int,rs}$) and chest wall ($R_{int,w}$), respectively. Finally, $P_{rs,st}$ and $P_{w,st}$ divided by the inflation volume yield the elastance of the respiratory system ($E_{rs,st}$) and chest wall ($E_{w,st}$), respectively. For the lung, the various parameters were computed as the difference between corresponding values of the respiratory system and the chest wall.

In seven subjects, the total inspiratory work per breath (W_I) and its components, namely static work (W_{st}), dynamic work due to viscous resistance (W_{dyn}) and additional tissue resistance (ΔW), were assessed as previously described [12, 13, 15]. To this end, P_{max} , P_1 and $P_{rs,st}$ were also measured during 3–4 breaths in which the inflation volume was reduced to 0.27 ± 0.03 and 0.14 ± 0.03 L, respectively, while keeping inflation flow unchanged. All these measures were taken at ZEEP.

In order to take into account the effects of anaesthesia and paralysis, the predicted normal values for VC in awake, supine subjects from QUANJER [16] were corrected according to the following equation computed from data obtained by JUNO *et al.* [17]:

$$\text{Change in VC } (\Delta VC) = 23.9 - 0.074 \cdot \text{age} - 90.7 \cdot \text{weight/height}$$

where the reduction of VC is expressed as a percentage of VC while awake and supine, age is expressed in years, weight in kilograms, and height in centimetres.

Values are presented as mean \pm SD. Regression analysis was performed using the least-square method and analysis of variance (ANOVA). Comparison with data obtained in ARDS patients without AIDS and PCP or normal subjects was made by means of Student's unpaired t-test, and a p-value of less than or equal to 0.05 was accepted as statistically significant. Such comparisons were made with previous results on ARDS patients [18–23] and normal subjects [12] obtained under similar ventilator settings to those of the present study.

Results

The average value of the $P_{a,O_2}/F_{I,O_2}$ ratio was rather low in the present patients (table 1). Indeed, mean arterial P_{a,O_2} was only 10 ± 2 kPa (76 ± 16 mmHg), in spite of the relatively high F_{I,O_2} (0.87 ± 0.21).

In all patients, VC was markedly reduced (1.54 ± 0.30 and 1.55 ± 0.32 L for the ZEEP and PEEP group, respectively). These corresponded to 35.6 ± 7.5 and $40.5 \pm 8.7\%$ of the predicted values, and did not differ significantly from each other.

Figure 1 shows the relationship between lung volume, expressed as a percentage of measured VC, and P_{tr} observed under static conditions in the ZEEP and PEEP group, respectively. Tidal ventilation occurred between 17 ± 5 and $48 \pm 7\%$ VC in the ZEEP group, and between 28 ± 10 and $59 \pm 17\%$ VC in the PEEP group. These two relationships were almost superimposed along the same volume-pressure (V - P) function, suggesting that low levels of PEEP do not change the mechanical characteristics of the respiratory system in AIDS patients

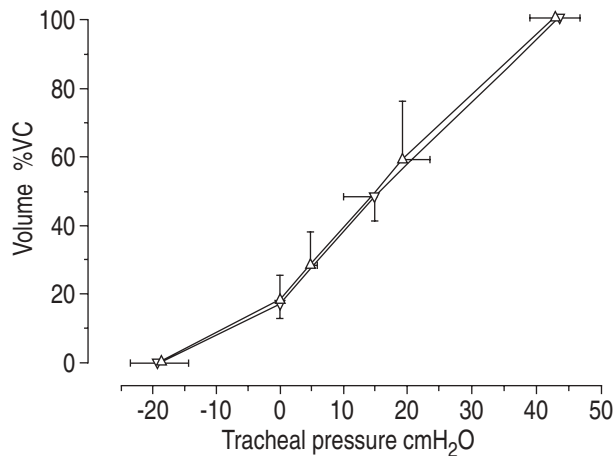


Fig. 1. — Average static volume-pressure relationships of relaxed respiratory systems in four patients at zero end-expiratory pressure (ZEEP; ▽) and eight patients on 4.9 cmH₂O positive end-expiratory pressure (PEEP; △). VC: vital capacity. Values are mean±SD.

with PCP. Because of this, and since no statistical difference was found for any mechanical parameter between the ZEEP and PEEP group, the data from the two groups were pooled; these mean values are reported in table 2 for the respiratory system, and in table 3 for the lung and chest wall.

The values of $E_{rs,st}$ and $E_{rs,dyn}$ were $36.2±8.8$ and $43.9±11.1$ cmH₂O·L⁻¹, and those of $R_{int,rs}$ and additional resistance of the respiratory system ($ΔR_{rs}$) $4.8±3.9$ and $6.8±3.1$ cmH₂O·s·L⁻¹, respectively. The values of $E_{w,st}$ and $E_{w,dyn}$ were $6.8±4.1$ and $8.2±3.9$ cmH₂O·L⁻¹, and those of $R_{int,w}$ and $ΔR_w$ $0.3±0.1$ and $1.2±0.4$ cmH₂O·L⁻¹, respectively. The values of static and dynamic elastance of the lung ($E_{L,st}$ and $E_{L,dyn}$, respectively) were $29.4±8.1$ and $35.7±10.7$ cmH₂O·L⁻¹, while interrupter resistance

of the lung ($R_{int,L}$) and additional resistance of the lung ($ΔR_L$) amounted to $4.5±3.8$ and $5.6±2.9$ cmH₂O·s·L⁻¹, respectively.

Inspiratory work

Figure 2 illustrates the relationship of changes in volume to those in tracheal and oesophageal dynamic pressure (P_{dyn}) during inflation at baseline tidal volume obtained in a representative patient. The inspiratory work done on the respiratory system (W_{rs}) and chest

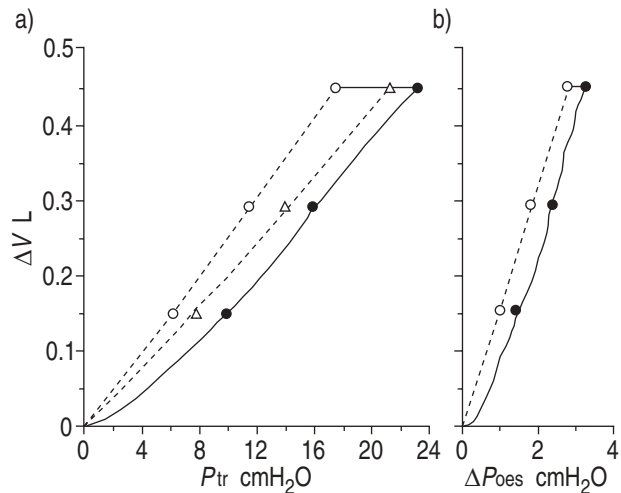


Fig. 2. — Measurements, in a representative patient, of: a) tracheal pressure (P_{tr}); and b) oesophageal pressure (P_{oes}), as a function of inflation volume ($ΔV$). ●: dynamic pressure; ○: static pressure; △: pressure at airway occlusion; —: curve obtained during constant flow inflation; - - -: curve obtained by linear interpolation between experimental points.

Table 2. — Static elastance (E_{st}), interrupter resistance (R_{int}), and additional resistance of respiratory system ($ΔR_{rs}$) in acute respiratory distress syndrome (ARDS) patients and normal subjects

[Ref.]	Subject condition	Age yrs	Subjects n	PEEP cmH ₂ O	PEEP _i cmH ₂ O	E_{st} cmH ₂ O·L ⁻¹	R_{int} cmH ₂ O·s·L ⁻¹	$ΔR_{rs}$ cmH ₂ O·s·L ⁻¹
Present study	ARDS	38±8	12	0–5	0	36.2±8.8***	4.8±3.9*	6.8±3.1***
[18]	ARDS	39±19	7	0	0	33.5±6.6***	1.7±1.0	3.8±1.8+
[19]	ARDS	61±11	8	0	-	32.2±7.9***	4.7±1.1***	8.8±2.9***
[20]	ARDS	33±16	11	5	0	41.5±16.8***	2.1±0.8	3.1±1.2+
[21]	ARDS	54±20	6	0	4.6±6.1	30.9±13.4**	4.2±1.9*	7.0±2.4***
[22]	ARDS	61±9	9	5	3.5±0.3	31.6±8.4***	5.0±1.2***	8.5±3.0***
[23]	ARDS	62±10	8	5	0	36.2±8.7***	3.9±1.9*	5.2±1.1***
[12]	Normal	31±8	16	0	0	14.6±2.2	2.2±0.5	2.9±0.8

Values are mean±SD. PEEP: positive end-expiratory pressure; PEEP_i: intrinsic positive end-expiratory pressure; *, **, ***: p<0.05, p<0.01, p<0.001, compared to normal values; +: significantly higher (p<0.01) than values for normal subjects obtained in the same study.

Table 3. — Static elastance (E_{st}), interrupter resistance (R_{int}), and additional resistance ($ΔR$) of lung and chest wall in acute respiratory distress syndrome (ARDS) patients and normal subjects

[Ref.]	Subject condition	Age yrs	Subjects n	Lung			Chest wall		
				E_{st} cmH ₂ O·L ⁻¹	R_{int} cmH ₂ O·s·L ⁻¹	$ΔR$ cmH ₂ O·s·L ⁻¹	E_{st} cmH ₂ O·L ⁻¹	R_{int} cmH ₂ O·s·L ⁻¹	$ΔR$ cmH ₂ O·s·L ⁻¹
Present study	ARDS	38±8	12	29.4±8.1***	4.5±3.8***	5.6±2.9***	6.8±4.1	0.3±0.1	1.2±0.4
[23]	ARDS	62±10	8	23.7±5.5***	4.4±1.9***	3.2±0.8***	13.2±5.4**		1.5±0.9
[13]*	Normal	30±8	18	7.9±1.6	1.1±0.4	1.9±0.6	6.1±1.0	0.4±0.1	1.1±0.2

Values are mean±SD. *: except for R_{int} which is from D'ANGELO *et al.* [14]; **, ***: p<0.01, p<0.001, compared to normal values.

wall (W_w) was computed as the areas subtended by these curves, while that done on the lung (W_L) was computed as difference ($W_{rs}-W_w$). Also shown in the figure are the relationships obtained by joining the change in volume of gas (ΔV)-static pressure (P_{st}) and ΔV - P_1 data points obtained during airway occlusions performed at different inflation volumes. Total W_{rs} and W_w was thus partitioned into a static component (W_{st}) given by the area subtended by the ΔV - P_{st} relationships, and a dynamic component (W_{dyn}) obtained as the difference between total inspiratory work and W_{st} . The static and dynamic components of work done on the lung ($W_{st,L}$ and $W_{dyn,L}$, respectively) were computed as $W_{st,rs}-W_{st,w}$ and $W_{dyn,rs}-W_{dyn,w}$, respectively. Dynamic W_{rs} was further partitioned into two components by the ΔV - P_1 relationship, the difference between P_{dyn} and P_1 along the horizontal axis representing the immediate drop in pressure after airway occlusion, and that between P_1 and P_{st} the slow decay during the occlusion. The area enclosed between the ΔV -tracheal P_{dyn} ($P_{dyn,tr}$) and ΔV -tracheal P_1 ($P_{1,tr}$) relationships should essentially represent work done to overcome airway resistance (W_{aw}) [13, 24], whilst the difference between $W_{dyn,rs}$ and W_{aw} reflects the additional work (ΔW_{rs}) done on the respiratory system as a result of time constant inequality and viscoelastic tissue behaviour [12]. Because no immediate drop was discernible on the P_{oes} tracings of single airway occlusions and hence no ΔV - P_1 relationship could be drawn for the chest wall, dynamic inspiratory pressure of the chest wall ($W_{l,dyn,w}$) should essentially represent the additional work done on the chest wall (ΔW_w). Finally, the additional inspiratory work done on the lung (ΔW_L) was computed as $\Delta W_{rs}-\Delta W_w$.

The individual values for total inspiratory work and its components are reported in table 4 and in figure 3a together with the corresponding values obtained in 18 normal anaesthetized, paralysed subjects under similar ventilator settings of the present study [13]. Also shown on the right ordinate of figure 3 is the total inspiratory work per litre (W_i/V_T). Because W_i is the product of mean pressure applied during inspiration (\bar{P}_I) and V_T , W_i/V_T corresponds to \bar{P}_I with respect to volume. Furthermore, because during constant flow inflation $V_T = \text{inspiratory flow (V'I)} \cdot \text{inspiratory time (tI)}$, W_i/V_T also describes \bar{P}_I with respect to the duration of inspiration.

The results in table 4 and figure 3a do not include the inspiratory resistive work due to the endotracheal tubes (W_{et}). During constant flow inflation, W_{et} is equal to resistance of the endotracheal tubes at a given flow (R_{et}) $\cdot V'I \cdot V_T$. Using the pressure-flow relationships of endotracheal tubes of various internal diameters and standard length (including connectors) measured *in vitro*,

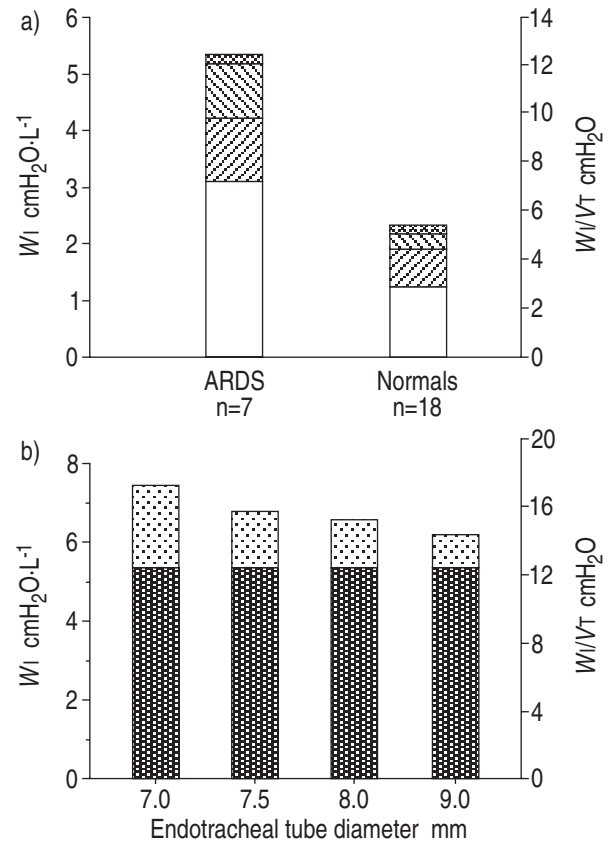


Fig. 3. – a) Mean values of total inspiratory work per breath (W_i) and its components in seven acute respiratory distress syndrome (ARDS) patients and 18 normal anaesthetized, paralysed subjects [13] on zero end-expiratory pressure (ZEEP) with inspiratory flow ($V'I$) of $0.57 \text{ L} \cdot \text{s}^{-1}$ and tidal volume (V_T) of 0.43 L . \square : static component of work done on the respiratory system. Dynamic work done on the respiratory system is the sum of work done to overcome airway resistance (cross-hatched) and additional work done on the lung (dotted) and chest wall (cross-hatched). b) Mean values of W_i , partitioned into work done on respiratory system (dotted) and endotracheal tubes (cross-hatched).

corresponding W_{et} values were determined for baseline $V'I$ ($0.57 \text{ L} \cdot \text{s}^{-1}$) and V_T (0.43 L), and were added to the average W_i value of the present patients to obtain the total inspiratory work per breath (fig. 3b). It should be noted that the latter represent theoretical values that would obtain if: a) the tubes had no concrete secretions or kinks that could alter their resistance; and b) the specified tubes had been used.

Discussion

Compared to normal, anaesthetized, paralysed subjects [12], the present patients exhibited a significantly

Table 4. – Inspiratory work done per breath on the respiratory system (W_{rs}), and components of the work done on the lung and chest wall during baseline mechanical ventilation in acute respiratory distress syndrome (ARDS) patients and normal subjects

Subjects	n	W_{rs} $\text{cmH}_2\text{O} \cdot \text{L}^{-1}$	W_{st}		ΔW		W_{aw} $\text{cmH}_2\text{O} \cdot \text{L}^{-1}$
			Lung $\text{cmH}_2\text{O} \cdot \text{L}^{-1}$	Chest wall $\text{cmH}_2\text{O} \cdot \text{L}^{-1}$	Lung $\text{cmH}_2\text{O} \cdot \text{L}^{-1}$	Chest wall $\text{cmH}_2\text{O} \cdot \text{L}^{-1}$	
ARDS	7	$5.36 \pm 1.34^{***}$	$2.65 \pm 0.55^{***}$	0.46 ± 0.17	$0.97 \pm 0.60^{***}$	0.15 ± 0.08	$1.12 \pm 0.66^*$
Normals ⁺	18	2.31 ± 0.11	0.71 ± 0.06	0.53 ± 0.07	0.26 ± 0.08	0.14 ± 0.03	0.67 ± 0.09

Values are mean \pm SD. ⁺: from D'ANGELO *et al.* [13]; *, ***, $p < 0.05$, $p < 0.001$, compared to normal values. W_{st} : static work; ΔW : additional work; W_{aw} : work done to overcome airway resistance; W_{rs} : work done on the respiratory system.

increased static elastance and total resistance of the respiratory system, the latter reflecting an increase of R_{int} and, particularly, of the additional resistance (ΔR) (table 2).

Static inflation V-P curve

None of our patients exhibited a clearly discernible inflection point on the static inflation *V-P* curve (figs. 1 and 2). According to some authors [25–27], in ARDS patients without AIDS and PCP the inflection point is a common occurrence, though this might not be particularly frequent according to other studies [22, 28–30]. It has been suggested that the inflection is present in the earliest stage of ARDS, whereas later on, probably as a result of oedema resolution, the inflection disappears with or without increases or decreases in elastance, probably depending on the pattern of fibrosis development [26]. Our patients may represent a relatively late stage of ARDS, in spite of the fact that the duration of intubation was short (table 1). Indeed, some reported respiratory symptoms such as cough and increased secretions prior to intubation, and two had had a previous episode requiring mechanical ventilation. On the other hand, it is conceivable that, owing to the peculiar pathogenetic pathways of AIDS-related PCP, inflection points never occur in the static inflation *V-P* curve of these patients. In fact, the pathological findings of PCP in AIDS patients include interstitial infiltrates associated with alveolar occupation by eosinophilic exudates, hyaline membranes, macrophages, and cellular debris, which oppose recruitment, whilst oedema is moderate or absent [8, 9]. Moreover, computed tomography scan performed in eight of our patients exhibited homogeneous diffuse interstitial and alveolar infiltration, at variance with what appears to be the most common finding in ARDS patients in whom dense opacities are mainly confined to the dependent lung regions [27]. Because the presence of an inflection point is taken to indicate alveolar recruitment, the present findings suggest that in AIDS patients with ARDS and PCP there is no substantial alveolar recruitment during lung inflation. An alternative explanation is that the recruited areas have a markedly higher elastance than the already ventilated alveoli, though it is difficult to conceive how the sequence of alveolar recruitment could be determined by local elastances in such a way that a lower elastance results in earlier recruitment.

Recently, to prevent low "volume barotrauma" due to mechanical stresses in the event of opening and closing of small airways with each breathing cycle, it has been proposed that in ARDS the applied PEEP should correspond to the pressure at the inflection point [31]. The absence of the inflection point in AIDS patients with PCP does not allow such an adjustment. Thus, in these patients the usefulness of PEEP remains to be established.

Elastance and resistance

The marked increase of $E_{rs,st}$ is in line with all previous studies on ARDS patients [18–23]. In our patients,

the increase of $E_{rs,st}$ was entirely due to increased $E_{st,L}$ while $E_{st,w}$ remained within normal limits (table 3). On the other hand, a marked increase of $E_{st,w}$ was found in ARDS patients by PELOSI *et al.* [23]; this may reflect different study populations or methodological discrepancies. It is also possible that, as a result of the possible difference in the distribution of lesions within the lungs (see above), the expansion of the chest wall in the patients of PELOSI *et al.* [23] occurred with greater distortion than in those of the present study.

The marked increase of ΔR_{rs} and R_{int} , the latter mainly reflecting increased airway resistance (R_{aw}), is in line with most studies on ARDS patients [19, 21–23]. In two previous studies [18, 20], however, both R_{int} and ΔR_{rs} did not differ significantly from the results obtained on normal, anaesthetized, paralysed subjects by D'ANGELO *et al.* [12]. The lower values of ΔR_{rs} found by AULER *et al.* [18] and PESENTI *et al.* [20] are probably due in part to differences in data analysis, since these ΔR_{rs} values were in any case significantly larger than those obtained by the same authors on normal, anaesthetized, paralysed subjects. Indeed, in the study of AULER *et al.* [18], computation of the slow decay of P_{tr} was limited to the first second following the rapid end-inspiratory airway occlusion. However, differences in patient population may also be responsible for the discrepant results, particularly in respect to R_{int} .

In the patients of the present study the values of $E_{rs,st}$ and ΔR_{rs} were similar at ZEEP and PEEP of 5 cmH₂O. This is consistent with the findings in normal subjects [32] and in ARDS patients [22, 23, 28, 29] obtained over a larger PEEP range, but contrasts with the results of FALKE *et al.* [25], who found a decrease in static elastance (E_{st}) with PEEP of 5 cmH₂O. The lack of $E_{rs,st}$ changes with PEEP in the present patients is not surprising because, like normal subjects, they did not exhibit an inflection point on the static inflation *V-P* curve (figs. 1 and 2) and, as a consequence, there probably was little or no alveolar recruitment with PEEP. On the other hand, in most of the ARDS patients in whom there was evidence of alveolar recruitment with PEEP [22, 23, 28, 29], $E_{rs,st}$ did not change significantly with PEEP of 5–10 cmH₂O, and $P_{rs,st}$ at end-inflation was not in the flat portion of the static inflation *V-P* relationship.

The values of R_{int} in the present patients were also independent of PEEP. This is at variance with findings in normal, anaesthetized, paralysed subjects [12, 14], but consistent with previous observations in ARDS patients [19, 20]. This discrepancy cannot be attributed to $R_{int,w}$ because in our patients it was both small and unaffected by PEEP (table 3). It is possible that because of the relatively high lung recoil in ARDS patients, further increases in lung volume and $P_{st,L}$ have little effect on the already stretched airways.

In all patients, VC was markedly reduced, as expected in ARDS. Because of absence of inflection points in the static inflation *V-P* curve, lung units ventilated over the VT range should be essentially the same as those ventilated over VC. From the reduction in VC, it is, therefore, possible to predict the increase in $E_{st,L}$ and $R_{int,L}$ relative to normal values [13, 14], on the assumption that the specific mechanical properties of the lung and airways remain normal (fig. 4). On this basis it can

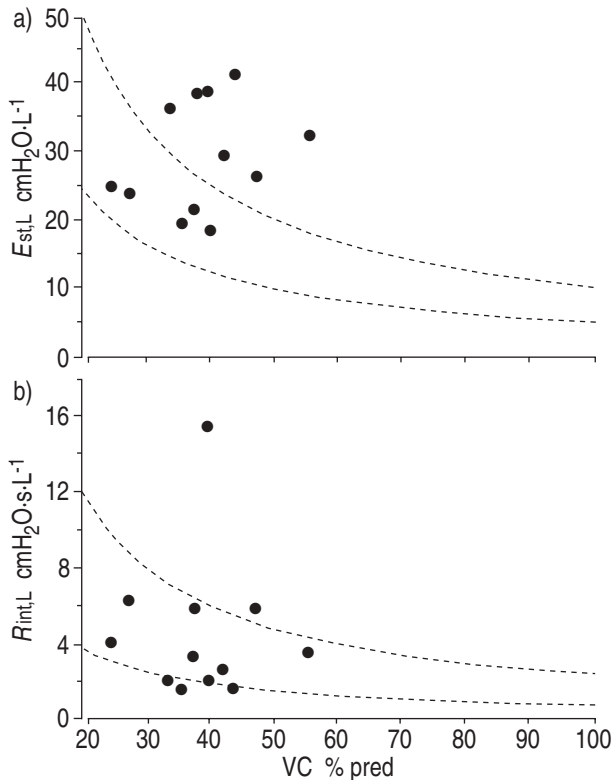


Fig. 4. — Relationship of vital capacity (VC) expressed as percentage of predicted values (% pred) to: a) static lung elastance ($E_{st,L}$); and b) interrupter resistance ($R_{int,L}$), in 12 patients. - - -: 95% confidence limits of the relationship expected with normal $E_{st,L}$ and $R_{int,L}$ (see text for further details).

be concluded that: 1) in five patients the aerated lung units retained nearly normal elastic properties, while in the other seven patients they became stiffer; and 2) airway resistance remained essentially normal in nine patients, increased in two patients, and probably decreased in one patient. Higher than expected values of $E_{st,L}$ could reflect fibrosis [6–10] and/or altered surfactant [33], while the contrasting changes in $R_{int,L}$ could reflect the interaction of multiple factors (increased lung recoil, release of bronchoconstrictor or bronchodilating agents, intraluminal secretions, peribronchial oedema or infiltrates). That multiple factors with opposite effects were modulating the airway resistance of our patients, besides a reduction in ventilated lung units, is also suggested by the absence of a significant correlation between $E_{st,L}$ and $R_{int,L}$ (fig. 5). This, in turn, may explain the occasional finding of an unchanged R_{int} in ARDS patients [18, 20].

The increase of ΔR_{rs} and ΔRL found in both the present patients, and in others with ARDS, (tables 2 and 3) may also be explained on the basis of the reduction of ventilated lung tissue, because the significant linear relationship between $E_{st,L}$ and ΔRL in figure 5 implies an inverse relationship between VC as a percentage of predicted and ΔRL . On the other hand, the correlation coefficient of the former relationship was rather low, suggesting that different factors may affect lung elasticity and viscoelasticity. Therefore, the elastance and the pressure dissipations within the lung tissue may not be inherently coupled, as previously suggested [34].

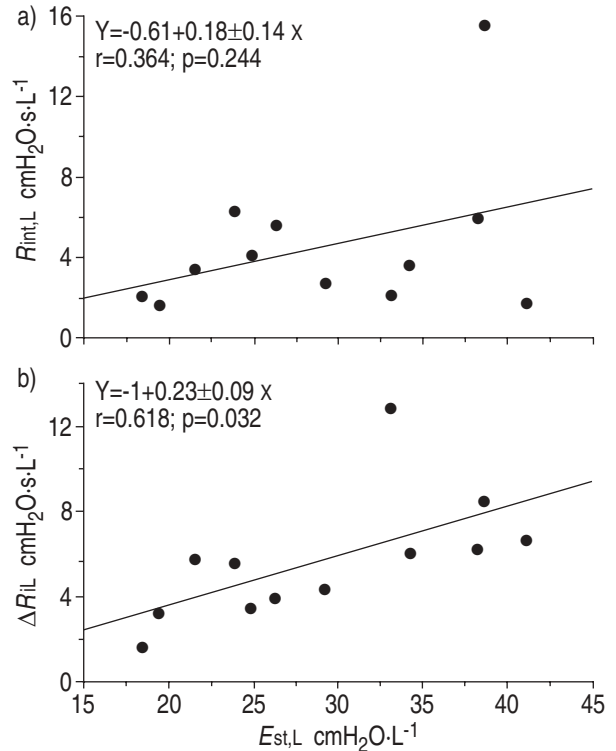


Fig. 5. — Relationship of static lung elastance ($E_{st,L}$) to: a) interrupter lung resistance ($R_{int,L}$); and b) additional resistance (ΔRL), in 12 patients.

Implications on inspiratory muscle fatigue

During baseline ventilation W_I was, on average, 133% higher in the present ARDS patients than in normal subjects (fig. 3 and table 4). This difference was largely due to increased $W_{st,rs}$ though both W_{aw} and ΔWL were also increased. By contrast, both $W_{st,w}$ and ΔW_w did not change significantly.

BELLEMARE and GRASSINO [35] have shown that the fatigue threshold of the diaphragm depends on its tension-time index (T_{tdi}) and that $T_{tdi} = (\bar{P}_{di} \cdot t_i / t_{tot}) / P_{di,max}$, where \bar{P}_{di} is the mean transdiaphragmatic pressure developed during inspiration, $P_{di,max}$ is the maximal static pressure at functional residual capacity, and t_i / t_{tot} is the inspiratory duty cycle. When T_{tdi} exceeds a critical value of ~ 0.15 , diaphragmatic fatigue is likely to occur. For the inspiratory muscles other than the diaphragm the tension-time index (T_{trcm}) = (mean pleural pressure (\bar{P}_{pl}) $\cdot t_i / t_{tot}$) / maximal pleural pressure ($P_{pl,max}$), and has a critical value of ~ 0.30 [36]. According to the data in figure 3b, the values of \bar{P}_I required to sustain the baseline ventilation during spontaneous breathing before intubation should have been $\sim 13 \text{ cmH}_2\text{O}$, while, given the partition of W_I in table 4, those of \bar{P}_{di} and \bar{P}_{pl} should have amounted to ~ 13 and $11 \text{ cmH}_2\text{O}$, respectively. Assuming the usual value of t_i / t_{tot} of 0.4, muscle fatigue would have occurred if $P_{di,max}$ and $P_{pl,max}$ were about 35 and 15 cmH_2O , respectively. These predicted values are considerably lower than those that can actually be developed by normal adults of a similar age to the present patients. Though most of these patients had a reduced muscular mass and were malnourished, as evidenced by low body weight and low plasmatic levels of albumin ($2.2 \pm 0.2 \text{ g}\cdot 100 \text{ mL}^{-1}$), it is unlikely that

mechanical ventilation was required because of impending inspiratory muscle fatigue. In fact, mechanical ventilation was instituted because of severe hypoxaemia, tachypnoea and dyspnoea.

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