Respiratory resistance and intrinsic positive end-expiratory pressure (PEEPi) in patients with the adult respiratory distress syndrome (ARDS)

C. Broseghini, R. Brandolese, R. Poggi, M. Bernasconi, E. Manzin, A. Rossi

Respiratory resistance and intrinsic positive end-expiratory pressure (PEEPi) is present during occlusion and end-inspiratory and end-expiratory airway pressure; it is the simplest and yields repeatable results. However, a wide range of volumes, with a giant syringe; 3) measurement of volume with the interrupter technique. The first method is the pulmonary function in patients with the adult respiratory distress syndrome (ARDS), because the added resistance of the endotracheal tubes and ventilator tubes is flow dependent, and averaged 13.2±2.9 cmH₂O·L·s⁻¹. These results indicate that in ARDS patients: 1) respiratory resistance may be increased and exhibit a marked frequency-dependence; 2) expiratory flow may be retarded by the increased expiratory resistance and/or by the added resistance of the endotracheal and ventilator tubes, and therefore PEEPi can be present despite the high driving pressure for expiration due to the stiff lung (Cst, averaged 0.037±0.010 cmH₂O·L⁻¹); 3) a significant error in the measurement of compliance is the consequence of an undetected and unmeasured PEEPi.

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The static compliance of the total respiratory system (Cst) is the variable most extensively used to assess pulmonary function in patients with the adult respiratory distress syndrome (ARDS), during mechanical ventilation [1-3].

Cst can be measured by three methods: 1) as the ratio between tidal volume (Vt) and the difference between a "plateau" pressure during airway occlusion at end-inspiration and end-expiratory airway pressure [1]; 2) by stepwise inflation and deflation of the lung over a wide range of volumes, with a giant syringe [4]; 3) with the interrupter technique [5]. The first method is the most common in the intensive care unit (ICU), because it is the simplest and yields repeatable results. However, measurement of Cst by means of end-inspiratory occlusion may lead to a significant underestimation of the "true" compliance, when an "intrinsic" positive end-expiratory pressure (PEEPi) is present during mechanical ventilation [6-8].

PEEPi is a common finding in patients with acute exacerbation of chronic obstructive pulmonary disease (COPD), but was also observed in patients with acute respiratory failure (ARF) without a history of chronic airway disease [7, 8]. In fact, expiratory flow could be retarded either by increased expiratory resistance, for example related to lung injury [9, 10], and/or by the added flow resistance of the endotracheal tubes, ventilator tubings, and attached devices.

In view of the importance of a correct measurement of Cst in ARDS patients [1], we undertook this study: 1) to assess and measure PEEPi; 2) to quantify the effect of unrecognized PEEPi on measurement of Cst; 3) to measure the total airflow resistance and to partition between respiratory (intrinsic) resistance and the added resistance of endotracheal and ventilator tubings.

Furthermore, because the application of PEEP is important in the management of ARDS [1], we examined the effect of PEEP on respiratory resistance and compliance in some ARDS patients with PEEPi.
Patients and methods

Fourteen consecutive ARDS patients were recruited for this study. They had been admitted to the ICU of the City Hospital in Padua, during a ten-month period of observation, because they needed mechanical ventilation. The research protocol was approved by the Ethical Committee of the Hospital. Informed consent was obtained from the next of kin of the patient.

The diagnosis of ARDS met standard criteria: 1) bilateral infiltrates on chest X-ray; 2) arterial oxygen tension (Pao₂) less than 50 mmHg with a fraction of inspired oxygen (Fio₂) of 0.5; 3) presence of one or more risk factors; 4) no history of chronic pulmonary disease; 5) no clinical suspicion of cardiogenic pulmonary oedema. The aetiology of ARDS, as well as patients' characteristics and final outcome are listed in table 1. Mean age was 44±18 yrs, ranging from 18-70 yrs.

All patients were intubated (Portex cuffed endotracheal tube (ETT), internal diameter from 7-8.5 mm), and mechanically ventilated with constant inspiratory flow on the control mode, which was obtained with 100% IMV (intermittent mandatory ventilation), using a Servo 900C ventilator (Siemens). All patients had a brief end-inspiratory pause. Settings of mechanical ventilation were established by the primary physicians according to their clinical judgement (table 2).

Patients were sedated (morphine) and eight of them were paralysed (pancuronium bromide) upon the decision of the primary physicians. No patient was sedated or paralysed because of our experimental protocol, and no change was made in the ventilatory settings during the study. All patients were examined as soon as possible after the onset of mechanical ventilation (within 24 h in all instances) and, with one exception (patient no. 13, table 1), before any PEEP had been applied, i.e. thirteen patients were examined on ZEEP (zero end-expiratory pressure). In patient no. 13, PEEP amounted to 15 cmH₂O.

Airway pressure (Paw) and flow (V) were measured with the pressure transducers of the Servo 900C; expired lung volume (Vr) was obtained by electrical integration of the flow signal [6]. All signals were calibrated independently and recorded throughout the study on a multichannel pen recorder (Mingograph Siemens) at a paper speed of 15.5 or 31 mm·s⁻¹.

Arterial blood gases were measured with an IL 1302 (Instrumentation Laboratories), and in table 2 average values are listed as they were found at the time of the study. Pao₂ and Fio₂ ranged from 38-183 mmHg and from 0.5-1, respectively. Pao₂/Fio₂ averaged 128.1±44.5.

Experimental procedure and data analysis

Patients were examined in the recumbent or semi-recumbent position, and a physician not involved in the procedure was always present to take care of the patient. After regular mechanical ventilation had been recorded for several breaths with the patient relaxed, airway occlusion was performed at the end of a mechanical lung inflation by means of the end-inspiratory hold button of the ventilator. After the occlusion, there was an immediate drop in Paw from the maximum value (Pmax) to a lower value (P₁), followed by a gradual decrease to an apparent plateau (P₂). After about 1.5-2 s, the occlusion was released. Under these conditions, P₂ represented the elastic recoil pressure of the total respiratory system at the end-inflation lung volume [11]. After another ten regular mechanical breaths, the end-expiratory airway occlusion was performed, using the end-expiratory hold button, at the end of a tidal expiration for direct measurement of PEEPi (fig. 1) [7]. Maneuvres were repeated three times for each patient at one-minute intervals to ensure a return to steady state between occlusions.

Cst was computed in two ways: 1) as the ratio between the expired tidal volume (Vr) and the difference between the end-inspiratory occlusion “plateau” and the unoccluded end-expiratory pressure, i.e. Cst=Vr/(P₂–PEEPi); 2) as the ratio between Vr and the differ-

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D: dead; S: survivor
ventilatory correspond to the resistance at very high dynamic impedance resulting from time constant inequalities within the lung and stress relaxation. $R_{rs}$ (Pmax - P1) by preceding constant flow (fig. 1), and subtracting the resistance of the endotracheal and ventilator tubing, the compliance of which amounted to 0.7 ml·cmH$_2$O$^{-1}$.

The end-inspiratory resistive properties of the respiratory system were obtained as previously described by Bates et al. [12] and Rosset et al. [13]. They showed that the "true" (i.e., ohmic) resistance of the respiratory system ($R_{rs_{meas}}$) is obtained by dividing the immediate drop in pressure following the end-inspiratory occlusion (Pmax - P1) by preceding constant flow (fig. 1), and subtracting the resistance of the endotracheal and ventilator tubes. By contrast, $R_{rs_{max}}$ is obtained by dividing Pmax - P1 by the preceding flow and subtracting the resistive component of endotracheal and ventilator tubes. $R_{rs_{max}}$ includes $R_{rs_{min}}$ and the "additional" inspiratory dynamic impedance resulting from time constant inequalities within the lung and stress relaxation. $R_{rs_{min}}$ should correspond to the resistance at very high frequency, whereas $R_{rs_{max}}$ reflects the resistance at very low frequency (i.e., near zero). Therefore the difference between $R_{rs_{max}}$ and $R_{rs_{min}}$ represents a simple way to determine the frequency-dependence of resistance. Both $R_{rs_{min}}$ and $R_{rs_{max}}$ were computed by subtracting from the total resistance (Rtot) the resistance of the endotracheal tube (Rett) and the resistance of ventilator tubing including the humidifier (Rcirc).

The pressure-flow relationship for both the endotracheal tubes and the ventilator tubing was curvilinear and fitted by a power function [13]. Therefore both Rett and Rcirc were flow dependent, and had to be computed for a given constant inspiratory flow (table 2). The final equation was:

$$R_{rs} = R_{tot} - (R_{ett} + R_{circ})$$

The ideal application of the end-inspiratory occlusion method would require an almost instantaneous occlusion of the airway opening, and hence an instantaneous drop of flow to zero. This was not the case in our study because of the finite occlusion time of the occlusion valve in the 900C Servo ventilator (fig. 1). The appropriate correction was made according to the technical considerations by Kocur et al. [14], and never exceeded 5% in this study.

In five patients with PEEPi ranging from 2–8 cmH$_2$O, after baseline measurements had been taken on ZEEP, PEEP was set by the ventilator and raised stepwise to 5, and 10 cmH$_2$O. Each step was maintained for 20 min to ensure a steady state [15], and measurements of respiratory mechanics repeated before the next level of PEEP.

Statistical analysis was performed with the two-tailed paired and unpaired t-test, and a least squares regression analysis. A value of p<0.05 was accepted as significant.

**Results**

Table 1 shows that in half of our patients an infectious factor, namely aspiration pneumonia or sepsis, was the aetiology of ARDS. Eight of the fourteen patients had a favourable outcome, regardless of infectious or non-infectious aetiology. However, both patients with ARDS due to aspiration pneumonia died. Seven patients were older than 40 yrs: among this group, only one patient survived in spite of an aetiology of sepsis, whereas, six of the seven patients younger than 40 yrs survived.

Mean ($\bar{x}$) data of respiratory mechanics are listed in table 3. PEEPi averaged 3.0±2.6 cmH$_2$O and was present
in ten of the fourteen ARDS patients, with a maximum of 8 cmH\textsubscript{2}O in one patient. Without the correction for PEEP, C\textsubscript{st,} averaged 0.033±0.010 l-cmH\textsubscript{2}O\textsuperscript{-1}. The mean corrected value was higher, i.e. 0.037±0.010 l-cmH\textsubscript{2}O\textsuperscript{-1} (p<0.001). The average error amounted to 13.9±10% in the fourteen patients, and 19.5±5.9% in the ten patients with PEEP with a range of 11–30% (fig. 2).

The mean value of \( R_{rs,\text{max}} \) and \( R_{rs,\text{min}} \) presented in table 3 reflects the resistance of the respiratory system, upper airway excluded, because the resistance of the endotracheal tube, ventilator tubing and humidifier was subtracted from the total. Figure 3 shows the mean value (so) of both minimum and maximum resistance \( (R_{rs,\text{min}} \) and \( R_{rs,\text{max}} \), respectively) before \( (R_{\text{tot}}) \) and after \( (R_{rs}) \) subtraction at any given flow of the resistance of the ventilator and endotracheal tubes. On average, the resistance of the endotracheal tubes and the inspiratory line of the ventilator (including the humidifier) taken together, amounted to 13.2±2.9 cmH\textsubscript{2}O l\textsuperscript{-1}s, representing 48 and 63% of \( R_{\text{tot, max}} \) and \( R_{\text{tot, min}} \), respectively (table 3, fig. 3). The mean (sd) normal value of \( R_{rs,\text{min}} \) is also shown in figure 3 (dotted area). It was measured in normal anaesthetized subjects using a method similar to the present one by Don and Robson [16], who, however, did not measure

<table>
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<td>PEEP (cmH\textsubscript{2}O)</td>
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PEEP: "intrinsic" positive end-expiratory pressure; C\textsubscript{st,}: static respiratory compliance; \( R_{rs,\text{min}} \) and \( R_{rs,\text{max}} \): maximum and minimum respiratory resistance after subtraction of the resistance of the endotracheal tubes and the inspiratory line of the ventilator.

Fig. 2. – Relationship between corrected and uncorrected static compliance \( (C_{st,}) \). Dots are individual measurements (average of three determinations); the continuous line is the identity line; the dashed lines are isopleths for slopes of 1.2 and 1.4.

Fig. 3. – Average values of minimum \( (R_{rs,\text{min}}) \) and maximum \( (R_{rs,\text{max}}) \) respiratory resistance with \( (R_{\text{tot}}) \) and without \( (R_{rs}) \) the resistance of the endotracheal and ventilator tubes. Dots are mean and bars standard deviation. The dotted area represents normal values (mean±sd) [16]. This figure also illustrates that the value of resistance calculated by a ventilator computer integrated system does not allow precise calculation, and that correction is required.

Rrs,\text{min}. In our ARDS patients both \( R_{rs,\text{min}} \) and \( R_{rs,\text{max}} \) were, on average, significantly higher than mean normal \( R_{rs,\text{min}} \) (p<0.05 and p<0.001), ranging between 1.8–17.7 cmH\textsubscript{2}O l\textsuperscript{-1}s, and 4.3–23.5 cmH\textsubscript{2}O l\textsuperscript{-1}s, respectively.

No significant correlation was found between individual values of total and respiratory resistance and the amount of PEEP (p>0.05).

The effect of PEEP on C\textsubscript{st,} and resistance for five patients with PEEP ranging between 2–8 cmH\textsubscript{2}O is shown in figure 4. With 5 cmH\textsubscript{2}O PEEP, the mean uncorrected C\textsubscript{st,} went from 0.033±0.006 to 0.035±0.010 l-cmH\textsubscript{2}O\textsuperscript{-1}, whereas the mean corrected C\textsubscript{st,} remained 0.037±0.008 l-cmH\textsubscript{2}O\textsuperscript{-1}. The average difference was 12% on PEEP and 6% on 5 cmH\textsubscript{2}O PEEP; PEEP reduced
PEEPi and therefore the error in measurement of Cst. At 10 cmH2O PEEP, there was essentially no PEEPi (less than 1 cmH2O, in two patients).

Both \( R_{rs_{\text{max}}} \) and \( R_{rs_{\text{min}}} \) were not significantly affected by PEEPi (fig. 4).

**Discussion**

The results of this study show that in ARDS patients, during the first 24 h of mechanical ventilation: 1) respiratory resistance may be increased with marked frequency-dependence; 2) a substantial added resistance is provided by the endotracheal tube, ventilator tubing and attached devices; 3) PEEPi is not uncommon and can lead to significant underestimation of static respiratory compliance.

Although it has been known since 1958 that pulmonary resistance can increase in patients with cardiogenic pulmonary edema [17], and has also been observed to increase in experimentally induced lung injury [10], measurement of pulmonary resistance is not a common practice in mechanically ventilated patients with cardiogenic pulmonary edema or ARDS. In our ARDS patients \( R_{rs_{\text{max}}} \) was increased, indicating, according to the analysis by BATTIS et al. [12], decreased bronchial calibre which could be due to fluid in the airway, and/or reversible bronchospasm [9, 18, 19]. On average, \( R_{rs_{\text{max}}} \) was almost twice \( R_{rs_{\text{min}}} \).

In line with the classical analysis by OTTS et al. [20], and its application to constant flow inflation by BATTIS et al. [12], increased \( R_{rs_{\text{max}}} \) includes the increased \( R_{rs_{\text{min}}} \) plus the additional peripheral component due to stress relaxation and time constant inhomogeneities within the lung. The mean difference between \( R_{rs_{\text{max}}} \) and \( R_{rs_{\text{min}}} \) in our ARDS patients amounted to 6.7±2.4 cmH2O-l-s, a value close to the 6.8±3.4 cmH2O-l-s, reported by ROSSI et al. [13] in their mechanically ventilated COPD patients, whereas 3.7±2.0 cmH2O-l-s was the \( R_{rs_{\text{max}}} - R_{rs_{\text{min}}} \) mean difference found by these authors in six mechanically ventilated patients without COPD [13]. COPD patients are well known to have frequency-dependence of resistance due to time constant inhomogeneities within the lung [21]. The possible rule of increased resistance and frequency-dependence of resistance in terms of gas exchange impairment and evolution of ARDS needs to be further clarified.

Figure 3 also shows how important the contribution of endotracheal tubes and ventilator devices is to total airflow resistance in mechanically ventilated patients. This suggests that the value of resistance provided by a ventilator-computer integrated system does not allow precise calculation of the resistance of the respiratory system, because it includes all added devices, the resistance of which is flow-dependent. This must be taken into account, i.e. correction is required, not only to compare patients who may have different sized endotracheal tubes and can be ventilated with different machines with different ventilator settings, but also to follow the evolution of lung disease in the same patient, in whom ventilator settings may be changed, either intentionally or as a result of a change in the patient's respiratory impedance.

Increased airway resistance due to lung injury, associated with the added resistance of endotracheal tube and ventilator devices, can prevent complete expiration and determine PEEPi in ARDS patients, even if a high recoil pressure, due to stiff lungs, is driving expiratory flow.

In mechanically ventilated patients there is no single respiratory time constant: in fact expiratory compliance may be linear throughout expiration, but resistance is always curvilinear, at least for the curvilinear pressure-flow relationship of the endotracheal tubes [5]. However, one could compute from mean values of \( C_{st} \) and \( R_{tot_{\text{max}}} \) (in table 3 and fig. 3) that an average expiratory time of 3 or more seconds would have been required to complete expiration, whereas the available expiratory time (Te) ranged from 1.4–3.4 s.

In ARDS patients, PEEPi is not necessarily an adverse phenomenon as it can be in COPD patients [7, 8]. In fact, modulation of expiratory time could represent a physiological way of applying a positive end-expiratory alveolar pressure in mechanically ventilated patients who are thought to need it for improvement of gas exchange. This improvement was actually observed and not satisfactorily explained in the past, with the application of inverse I:E ventilation, namely mechanical ventilation with a long inspiratory time and a much shorter expiratory duration. The short Te enhances PEEPi and may determine the same improvement in Pao2, which usually follows the application of PEEP by the ventilator [1]. However, the effects of PEEPi on gas exchange still needs to be investigated.

A low respiratory compliance is a well recognized pathophysiological characteristic of ARDS since the first description of the syndrome by ASHBLAGH et al. in 1967 [22]. These authors computed compliance as the ratio between tidal volume and maximum airway pressure, i.e. the "effective" compliance, which included both the elastic and resistive properties of the respiratory system. They found values ranging from 0.009–0.019 l-cmH2O. Static compliance is more frequently used as a reliable measurement of the respiratory elastic recoil, and in ARDS patients, changes in static respiratory compliance are generally accepted to reflect changes in lung elastic recoil [3]. Static respiratory compliance, therefore, became the most widely used functional variable to assess status and progress of the disease, as well as to improve mechanical ventilatory support [1, 2]. Our results show that detection and measurement of PEEPi is needed to obtain the correct value of \( C_{st} \) in ARDS patients.

However, although significant, the difference between the uncorrected and corrected (for PEEPi) \( C_{st} \), averaged about 20% in the ten patients with PEEPi, not exceeding 30% in the patient with the highest PEEPi. The magnitude of this error is unlikely to significantly affect the management of ARDS patients. In fact, as shown in figure 4 in five patients with PEEPi, there was little difference on average in the changes induced by PEEP on compliance, when either the uncorrected or corrected \( C_{st} \) was measured.
Figure 4 also shows that, in those five patients, respiratory resistance was not significantly affected by increasing PEEP. Suter and co-workers [2] [1] found that resistance progressively decreased slightly with PEEP by 0.3±0.1 cmH₂O·l⁻¹·s per cmH₂O PEEP. This difference probably reflects patients’ individual variability in response to PEEP.

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References


RÉSUMÉ: Quatorze patients consécutifs atteints de syndrome de détresse respiratoire aiguë ont été examinés dans 24 h après le début de la ventilation mécanique, pour déterminer leur résistance respiratoire (Rrs) et leur compliance (Cst), et pour déterminer l’influence de la pression positive en fin d’expiration (PEEP) sur les mesures de compliance. Le débit, la pression et les modifications de volumes pulmonaires, ont été mesurés au moyen des transducteurs du ventilateur Servo 900 C Siemens. L’occurrence des voies aériennes a été réalisée au moyen des bottons de fin d’inspiration et de fin d’expiration du ventilateur. Nous avons trouvé une PEEP de 3.02±2.6 cm H₂O·l⁻¹·s chez 10 des 14 patients. Sans correction pour la PEEP, la mesure de compliance Cst, était sous-estimée en moyenne de 13.9±10% pour l’ensemble des 14 patients, et en moyenne de 19.5±5.9% chez les 10 patients atteints de syndrome de détresse respiratoire aiguë et soumis à PEEP. La résistance respiratoire maximale et minimale (Rrs_max et Rrs_min), et la dépendance de la résistance à l’égard de la fréquence, ont également été mesurées. En moyenne, la résistance était fortement fréquence-dépendante, ainsi qu’en témoigne la différence entre Rrs_max et Rrs_min avec une augmentation à la fois de Rrs_max (7.7±4.2 cm H₂O·l⁻¹·s) et de Rrs_min (14.3±5.0 cm H₂O·l⁻¹·s). L’addition de résistance provenant du tube endo-trachéal et des tubes des ventilateurs était dépendante du débit, et atteignait en moyenne 13.2±2.9 cm H₂O·l⁻¹·s. Ces résultats indiquent que chez les patients atteints de syndrome de détresse respiratoire aiguë: 1) la résistance respiratoire peut être augmentée et manifeste une forte dépendance à l’égard de la fréquence; 2) le débit expiratoire peut être retardé, soit par l’augmentation de résistance respiratoire et/ou par la résistance ajoutée provenant des tubes endo-trachéaux et du ventilateur. Pour cette raison, la PEEP peut être présente, malgré la forte pression de propulsion pour l’expiration due au poumon rigide (Cst est en moyenne de 0.037±0.010 cmH₂O·l⁻¹); 3) une erreur significative dans la mesure de la compliance est la conséquence d’une PEEP non détectée et non mesurée.

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