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Effects of nebulized salbutamol on respiratory mechanics in adult respiratory distress syndrome

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Abstract *Objective:* To determine whether nebulized salbutamol improves the respiratory mechanics of patients with adult respiratory distress syndrome (ARDS). We also assessed the mechanisms that contribute to high respiratory system resistances during this disease. *Patients and setting:* Eleven consecutive patients with ARDS without clinical evidence of chronic obstructive pulmonary disease, admitted to a polivalent intensive care unit, and mechanically ventilated with Siemens Elema Servo C ventilator at constant inspiratory flow. *Method:* Peak airway pressure (Ppeak), airway pressure immediately after end inspiratory occlusion (P1), plateau pressure (P2) and intrinsic positive end-expiratory pressure (PEEPi) were measured at baseline condition and then 5, 15, and 30 min after 1 mg of salbutamol had been administered via a nebulizer through the endotracheal tube. Partial pressure of arterial oxygen (PaO_2), heart rate (HR) and mean blood pressure (BP) were monitored and minimal respiratory system resistances (Rrs, m), additional resistances (DRrs) and static compliance (Cst) were computed
Results: Between baseline and post-salbutamol, we observed changes in Ppeak, P1, P2, PEEPi and Rrs, m. As there were no significant differences between values at the different intervals during post administration, the results are described comparing baseline and 15 min post-salbutamol administration values. We found a significant decrease in Ppeak (4.9 ± 0.8 cmH_2O), P1 (3 ± 0.6 cmH_2O), P2 (2.1 ± 0.6 cmH_2O), PEEPi (1.9 ± 0.5 cmH_2O) and Rrs, m (1.9 ± 0.3 $cmH_2O/1\ s^{-1}$); DR, rs decreased in five patients, did not change in four and increased in two. HR, PaO_2 and BP did not change. *Conclusions:* a) Salbutamol administered through the endotracheal tube by a nebulizer device lessens respiratory system resistances and airway and alveolar pressures, and therefore could decrease the risk of barotrauma and alveolar damage; b) high respiratory system resistances in ARDS have an increased smooth muscle tone component that can be reversible with salbutamol.

Key words Adult respiratory distress syndrome · Bronchodilators agents · Barotrauma/salbutamol effect · Respiratory mechanics · Airway resistances · Intrinsic PEEP

Introduction

After the initial description by Ashbaugh [1], investigations in animal models suggested that the airflow resistances of the respiratory system could be significantly high in adult respiratory distress syndrome (ARDS). Moreover, recent studies in human patients with this syndrome [2–4] have proved that airflow and additional resistances are increased.

Although several authors [5–7] have studied the efficacy of bronchodilators (BD) in patients with chronic obstructive pulmonary disease (COPD) on mechanical ventilatory support, the action of these drugs on the pulmonary mechanics in ARDS, and their clinical consequences, have been analyzed in only a few studies [4, 8], in spite of their being extensively and empirically administered to these patients in intensive care units. The purpose of this study was to determine whether high respiratory resistances, low compliance and, in consequence, high airway pressure and air-trapping caused by positive pressure mechanical ventilation in ARDS patients could be reversed by administering salbutamol with a nebulizer device through the ventilator inspiratory circuit.

Material and methods

Study population

We studied 11 consecutive patients (1 woman and 10 men), admitted to the Intensive Care Unit of the Hospital "Juan Ramón Jiménez" of Huelva, Spain, between January 1992 and February 1993, placed on mechanical ventilatory support with Servo C ventilator (Siemens, Berlin, Germany) and with a diagnosis of ARDS because they met the following criteria: 1) known ARDS-associated predisposing factor or clinical condition, 2) partial pressure of arterial oxygen (PaO_2) less than 60 mmHg while they were breathing at least 40% oxygen or a ratio of PaO_2 to inspiratory fraction of oxygen (PaO_2/FIO_2) less than 150, independent of the level of positive end-expiratory pressure (PEEP), 3) diffuse bilateral infiltrates on chest radiograph compatible with pulmonary edema and 4) pulmonary artery wedge pressure less than 18 mmHg measured during an expiratory pause. Patients with a known history of COPD and those who had received BDs 6 h before the start of the procedure were excluded.

Table 1 Patients' clinical characteristics (*PCP Pneumocystis carinii pneumonia*)

Patient	Age	Sex	Disease	Murray score
1	60	W	Acute pancreatitis	2.75
2	20	M	Open thoracic wound	2.5
3	75	M	Aspiration pneumonia	2.75
4	65	M	Thoracic surgery	2.5
5	19	M	Thoracic trauma	3
6	51	M	Thoracic trauma	2.5
7	42	M	Nosocomial pneumonia	2.75
8	72	M	Aspiration pneumonia	2.5
9	36	M	PCP. AIDS	2.5
10	33	M	Ulcerative colitis; sepsis	2.75
11	64	M	Acute pancreatitis	2.75
x ± SE	49 ± 6			2.6 ± 0.1

This research was approved by the institutional Ethics Committee and consent was obtained from next of kin. The patients' clinical characteristics are summarized in Table 1. All patients were intubated by the orotracheal route, size 8–9 mm internal diameter tube cut to a length of 24 cm, were mechanically ventilated with constant inspiratory flow and sedated with midazolam with the aim of suppressing spontaneous respiratory efforts. Prior to the start of the procedure, if necessary, vecuronium (0.1 mg/kg) was administered to achieve this last objective. Patients' ventilatory parameters were kept constant throughout the procedure (Table 2).

The mechanical ventilatory support was set up by the primary physician not involved in the study, and not the researcher, in order to get an arterial blood pH between 7.35–7.45 and an arterial blood oxygen saturation (sat O_2) of more than 90%. Whenever possible, we removed PEEP 15 min before the procedure, with the primary physician's prior consent; a decrease in sat O_2 was corrected with higher FIO_2. This maneuver was executed so as not to interfere with the intrinsic positive end-expiratory pressure (PEEPi) measurement. We monitored electrocardiograph signals on a screen monitor, sat O_2 with a pulse oxymeter, arterial blood pressure (BP) with an indwelling intra-arterial catheter and pulmonary pressure with a pulmonary artery (Swan-Ganz) catheter. Prior to the start of each protocol, every patient was placed in a supine position and subjected

Table 2 Ventilatory parameters in the eleven patients during the procedure

Patient	Tube (mm)	Vt (ml)	RR (bpm)	iFlow (1/s)	PEEP (cmH_2O)	FIO_2
1	9	750	20	1.02	6	0.45
2	8.5	765	20	0.95	14	0.5
3	9	730	17	0.80	8	0.6
4	8.5	630	13	0.52	0	0.5
5	8.5	690	20	0.78	9	0.6
6	8.5	690	13	0.66	0	0.45
7	8	720	20	0.93	6	0.6
8	9	650	14	0.6	0	0.45
9	9	725	13	0.75	0	0.5
10	8.5	900	16	0.72	0	0.6
11	8.5	715	15	1.01	0	0.8
x ± SE	8.6 ± 0.1	723 ± 22	16.3 ± 1	0.7 ± 0.1		0.5 ± 0.1

to endotracheal suctioning. Throughout the procedure two physicians were present, one to attend to the patient's needs, in collaboration with a nurse, and another to collect research data.

Study protocol

We recorded airway flow and pressure waveform on a four channel polygraph (Mingograph, Siemens-Elema, Solna, Sweden); first, before administering the BD, and then 5 min, 15 min and 30 min after giving 5 mg of salbutamol (1 cc Ventolin and 3 cc saline). As a previous study [7] had proved that nebulized saline does not modify respiratory mechanics in patients with acute respiratory failure, the changes in the variables studied were attributed to the effect of salbutamol. The BDs were delivered in the form of a nebulized aerosol through the endotracheal tube, using a Siemens Servo Nebulizer 945 driver (Siemens-Elema, Solna, Sweden) connected to the inspiratory gas source. In order to avoid the additional volume generated by the nebulizer, the tidal volume was adjusted to the previous value during the administration, but basal and post-salbutamol measurements were taken without Servo nebulizer gas flow.

Arterial blood samples and gas measurements were taken at each of the four periods (baseline and 5, 15, and 30 min after BD). Firstly, we recorded between three and five regular breathing cycles and then an end-expiratory pause was performed by pressing the ventilator button in order to obtain PEEPi, as previously described [9, 10]. Subsequently we allowed at least two regular breathing cycles before causing an inspiratory pause by pushing the end inspiratory hold ventilator button; we obtained a sudden decrease in airway pressure, reaching a given value (P1) that corresponds to the necessary pressure to compensate inspiratory airway resistance to airflow and, afterwards, a slower fall until a plateau value (P2) was reached; this decrease results from the viscoelastic properties of the thoracic tissue and time-constant inequalities within the pulmonary units [3, 11]. P2 represents the elastic recoil pressure of the global respiratory system [12, 13] and, moreover, it provided further evidence of relaxation of the respiratory muscles.

Measurement of variables

We measured airway pressure and inspiratory flow on polygraphic curve records with graduated signals amplified to set a level of 2 cmH_2O/mm on the pressure curve and 2 l/min per mm on the flow curve. Volume measurements of each breathing cycle were obtained by the electrical integration of the analog output signal of Siemens 900 C flow sensor by means of an electronic device. We had to correct both gas compression and volume expansion in the tubes according to Siemens Elema manufacturer recommendations.

Computation of variables

Static respiratory compliance (*Cst*)*:* This was computed dividing the expiratory tidal volume by the difference between end-inspiratory occlusion (P2) and end-expiratory airway pressure (PEEP + PEEPi).

Inspiratory resistances: Respiratory system resistances were partitioned into minimum inspiratory resistances (Rrs, m) and additional resistances (DRrs) [3, 13]. The first was obtained by dividing the immediate airway pressure drop after end-inspiratory occlusion (Ppeak-P1) by the inspiratory flow, and this corresponded to the effective airway flow resistances, whereas DRrs was calculated by dividing the additional pressure fall after prolonging the inspiratory pause until a "plateau" (P1-P2) was reached, by the flow preceding the end-inspiratory interruption, this being a consequence of tissue resistance to inflation and time-constant inequalities [14, 15]. In the first case, we substracted tracheal tube resistances according to Rossi [12].

Statistical analysis

We performed a two-way analysis of variance and, in those cases where we found significant difference, we made comparisons between different stages by Student's paired *t*-test with the Bonferroni correction. We considered differences significant at $p < 0.05$.

Results

Table 2 shows the initial ventilatory parameters prescribed by the primary physician, except PEEP and FIO_2, which were prescribed by the researcher during the procedure. The average values ($\pm$ SE) of all measured or computed variables are listed in Table 3. They refer to the baseline state and to post-salbutamol administration (5, 15 and 30 min later). We will only refer to the differences between baseline state and 15 min post-salbutamol in order to simplify the description, because no statistical significance was found among the results at 5, 15 and 30 min. In five patients, the study was carried out with PEEP owing to the clinical impossibility of removing it. In the other cases, no patients needed FIO_2 higher than 0.8 to achieve the required sat O_2 ($> 90\%$).

Table 3 Average values of the variables studied at the four stages of the procedure. Comparisons are made between baseline values and 15 min post-salbutamol values (*$p < 0.01$; $^{+}p < 0.05$)

	Ppeak* (cmH_2O)	P1* (cmH_2O)	P2* (cmH_2O)	Rrs, m* (cmH_2O/ls^{-1})	DRrs (cmH_2O/ls^{-1})	PEEPi^{+} (cmH_2O)	Cst (ml/cmH_2O)	PaO_2 (mmHg)
Basal	43 $\pm$ 3.3	36 $\pm$ 2.5	30 $\pm$ 2.3	6.2 $\pm$ 1.4	7.1 $\pm$ 1.0	7.1 $\pm$ 0.9	32 $\pm$ 2.0	78 $\pm$ 5
5 min	38 $\pm$ 3.1	33 $\pm$ 2.4	28 $\pm$ 2.1	4.1 $\pm$ 1.5	6.3 $\pm$ 0.8	5.3 $\pm$ 1.1	34 $\pm$ 2.0	80 + 5
15 min	38 $\pm$ 3.0	33 $\pm$ 2.3	28 $\pm$ 2.0	3.9 $\pm$ 1.3	5.9 $\pm$ 1.1	5.3 $\pm$ 0.8	33 $\pm$ 2.0	79 $\pm$ 5
30 min	39 $\pm$ 3.1	33 $\pm$ 2.4	29 $\pm$ 2.1	4.0 $\pm$ 1.4	6.5 $\pm$ 1.2	5.7 $\pm$ 1.1	33 $\pm$ 1.7	81 $\pm$ 6

Airway pressures (Fig. 1)

A significant decrease in peak airway pressure (Ppeak) of 4.9 ± 0.8 cmH_2O was observed from 43 ± 3.3 to 38 ± 3.3 cmH_2O average values. P1 and P2 also decreased significantly after salbutamol administration (3 ± 0.6 and 2.1 ± 0.6 cmH_2O, respectively).

PEEPi (Fig. 2)

This was present in seven patients. It decreased slightly in all of them after salbutamol (1.85 ± 0.5 cmH_2O), although it did not disappear altogether. PEEPi was not present in four patients, but two of them needed PEEP levels of 8 and 9 cmH_2O during the protocol.

Respiratory system resistances (Fig. 2)

We obtained Rrs, m values at a baseline state of 6.2 ± 1.3 $cmH_2O/1\ s^{-1}$. After salbutamol was administered to our patients, Rrs, m significantly decreased

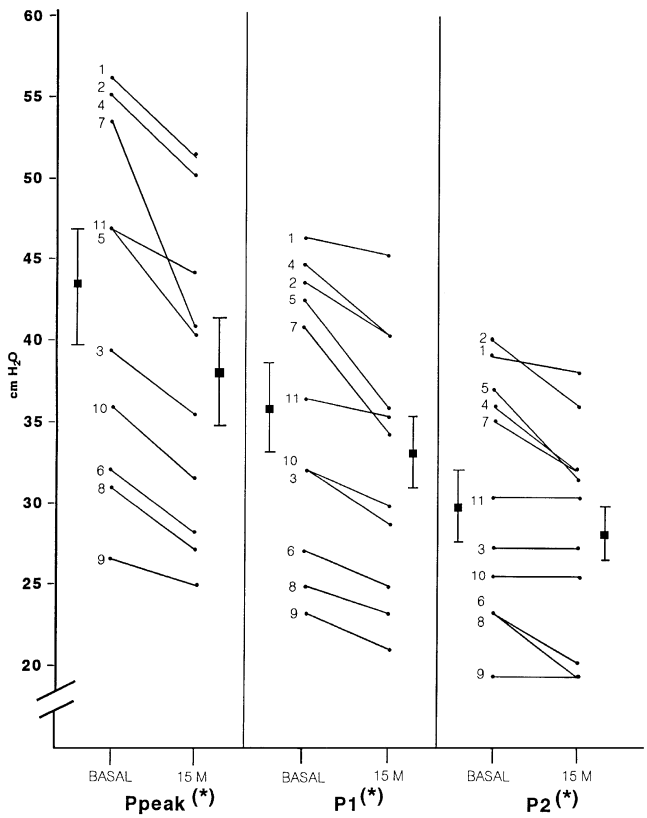

Fig. 1 Behavior of Ppeak, P1 and P2 after administering nebulized salbutamol. Individual patients data before and 15 min post-salbutamol are shown ($*p < 0.01$)

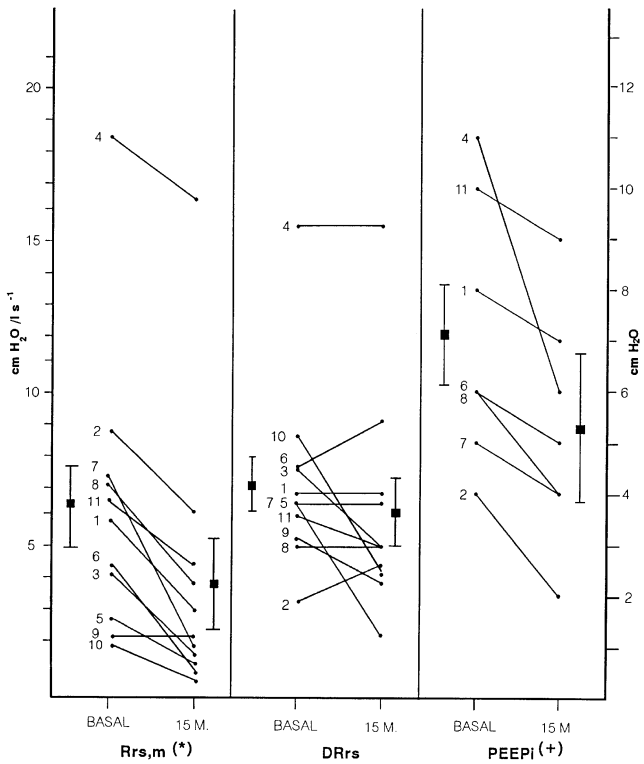

Fig. 2 Behavior of Rrs, m, DRrs and PEEPi after administering salbutamol. Individual patient data before and 15 min post-salbutamol are reported ($*p < 0.01$; $^{+}p < 0.05$)

1.9 ± 03 $cmH_2O/1\ s^{-1}$ (from 6.2 ± 1.3 to 3.9 ± 1.3 $cmH_2O/1\ s^{-1}$). Although DRrs decreased in five patients, it was not statistically significant when globally analyzed.

Cst, PaO_2, BP and HR

These did not change significantly after salbutamol administration. We did not observe any secondary effects that might be attributed to salbutamol.

Discussion

Observations from the present study reveal, on the one hand, as other authors have seen before [2, 3, 16], that respiratory system resistances are increased in ARDS patients and this fact could contribute, together with low compliance, to the characteristic respiratory mechanics of this syndrome; but on the other hand, show that the airway resistances and pressures of ARDS patients on mechanical ventilatory support are reduced after administering salbutamol with a nebulizer connected to the endotracheal tube; perhaps with fewer

secondary effects than intravenous route administration [4].

Since Gattinoni's work with tomographic scans [17] and research on techniques involving inert gases [18], we view ARDS as a bicompartmental model; this, although an over-simplification, explains the changes in pulmonary mechanics described in this entity. In accordance with this theory, a small amount of lung tissue with normal compliance and resistance would support the whole ventilatory volume, while the rest would be flooded by fluid edema and, therefore, unable to participate in gas exchange because of a shunt effect [19, 20]. The global result on lung mechanics would be an increase in airway resistance and a decrease in lung compliance.

As a result, we ventilated these patients with high minute volume and increased PEEP levels with the aim of reaching acceptable values of arterial blood gases; but this may have the adverse effect of generating very high pressure in airway and alveoli. Some studies have demonstrated that high alveolar pressure may be responsible for barotrauma [21], not only because of alveolar over-distension but also because it causes injuries to the capillary membrane of the alveoli [20, 22–26] leading to alveolar pulmonary edema indistinguishable from that of ARDS and self-perpetuating the respiratory failure. In this respect, Suchyta et al. [27] have recently suggested that the number of ARDS patients who die because of refractory respiratory failure may be higher than previously described. In addition, air-trapping, which is manifested as PEEPi, increases the risk of barotrauma, can contribute to hemodynamic instability and augments the work and oxygen cost of breathing is assisted ventilation and spontaneous breathing.

Peak pressure of the airway (Ppeak) has been the parameter statistically most closely related to the incidence of barotrauma in mechanically ventilated patients [28]. After salbutamol was administered, we found a significant decrease in Ppeak in all our patients (ranging between 3 and 12 cmH_2O). However, Ppeak depends on several factors, such as lung volume and the resistive and elastic properties of the respiratory system and circuit; therefore, it is not an appropriate parameter to use as a predictor of barotrauma, so we must analyze the behavior of each of its components, resistive pressures (Ppeak-P2) and elastic pressures (P2), independently.

Regarding resistances, our findings confirm that high respiratory resistances are an important component of the respiratory mechanics in ARDS patients [2, 3, 29, 30]. Our values are basally higher that those reported by Bernasconi and Pesenti, using the similar method [3, 4]. We attribute these differences to the varying degrees of severity in the condition of our patients and the fact that we did not substract equipment resistence. Rrs, m, which corresponds to pure airflow resistance [13], significantly decreased after administering salbutamol; therefore, it is possible that high airflow resistances in these patients are a consequence of a decreased number of permeable airways, but also of a high bronchomotor tone component that reduces the airway diameter. We have not definitely proved on which level BDs act, but following the bicompartmental model of ARDS, it may be possible that salbutamol acts in normally aereated lung tissue.

DRrs are also increased in ARDS, reflecting time-constant inequalities and the behavior of lung tissue, which adapts poorly to stress. We found, in contrast to Pesenti et al. [4], who administered salbutamol intravenously, a decrease in DRrs values in six patients, whereas four remained unchanged and in one the values actually increased; globally analyzed, they did not reach statistical significance. Salbutamol has demonstrated its usefulness as a BD in both central and peripheral airways [31]; thus, this finding implies that salbutamol may contribute to equalizing the time-constants of lung units and to reducing DRrs values, in this way, if we assume stress behavior is not modified.

The second component of Ppeak, P2 or elastic recoil pressure of the respiratory system in a static condition, corresponds to the highest alveolar pressure obtained during mechanical ventilatory support. In our study, we recorded a decrease between 1 and 6 cmH_2O, produced overall at the expense of a drop in PEEPi, and not because of an improvement in the elastic properties of lung tissue.

PEEPi decreased in all patients who showed it between 1 and 5 cmH_2O. Although statistically significant, this was less than we might have expected after such an important decrease in resistances; it is possible that mechanisms other than high ventilatory requirements and increased bronchial smooth muscle tone can contribute to PEEPi in ARDS. Among these are airway collapse, which may be a consequence of several anatomical and physiopathological changes present in these patients: loss of the elastic recoil pressure of lung parenchyma due to an inflammatory process inherent to ARDS; increased airway resistance that augments the pressure drop along the airway, facilitating the reversal of the transmural pressure gradient; mucosal edema, which augments forces tending to collapse the airways and, finally, reduced lung volumes. This mechanism of PEEPi would not be reversible with salbutamol and its improvement would depend on the repairing process of lung injuries. New studies designed using this hypothesis will be necessary to shed more light on this issue. Four patients did not show PEEPi; in two of them the measurement was made without PEEP, but in the other two high levels of PEEP were preset during the study. This fact might have interfered with the measurement of PEEPi by masking or

counterbalancing it and, as a result, the effect of salbutamol might not be evident. Cst did not improve significantly in spite of a drop in P2, because a similar fall in the level of PEEPi occurred after salbutamol, this being in accordance with the purely bronchodilating effect of salbutamol without affecting distensibility of lung tissue.

Determining the best ventilatory parameters to improve the effectiveness of nebulized drugs, among them PEEP, is an unresolved problem, and there is also no standard method to establish the best PEEP in this population. Consequently, we proposed withdrawing PEEP in order to introduce a lesser degree of inhomogeneity, except that which is inherent to ARDS. Following the criteria of the primary physician, PEEP was only withdrawn in patients 4, 6, 8–11. Although we think that PEEP, by increasing the accessible gas volume and opening collapsed airways, might increase the effectiveness of nebulized drugs in some patients, Figs. 1 and 2 showed that nebulized salbutamol was effective in both groups of patients, those ventilated with PEEP and those without PEEP.

In conclusion, we have shown that high respiratory system resistances in ARDS patients may be partially reversed with nebulized salbutamol, consequently lowering airway, end-inspiratory and-expiratory alveolar pressures; this fact may contribute to lessening the risk of barotrauma and alveolar injury, although future experiments are required to determine whether the morbidity, as a result of mechanical ventilation, in this group of patients is truly improved. In such a case it would be necessary to ascertain the most effective and suitable dose, interval and method of administration [32]. Meanwhile, we can recommend the use of salbutamol, taking into account the absence of secondary effects proved in our work.

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