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Dose-response effects and time course of effects of inhaled fenoterol on respiratory mechanics and arterial oxygen tension in mechanically ventilated patients with chronic airflow obstruction *

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Abstract. To investigate the dose-response relationship and the time course of the effects of fenoterol (a selective β_2-adrenergic agonist) on respiratory function in mechanically ventilated patients with acute respiratory failure due to exacerbation of chronic airflow obstruction (CAO), seven consecutive acutely ill patients were studied within 3 days of the onset of mechanical ventilation. Airflow, airway pressure, and changes in lung volume were measured with the transducers of the 900 C Servo Ventilator, the last by electronic integration. The end-expiratory lung volume (EELV), the intrinsic positive end-expiratory pressure ($PEEP_i$), the static respiratory compliance (Cst_{rs}), maximum and minimum respiratory resistance (Rrs_{max} and Rrs_{min}), and arterial oxygen tension (PaO_2), were measured under control conditions (all patients were receiving aminophylline infused at a constant rate) 5, 15, and 30 min after administration of 4 ml aerosolized saline solution and 5, 15, and 30 min after inhalation of 0.4, 0.8, and 1.2 mg fenoterol. After the last dose, measurements were repeated at 60, 120, and 180 min. We found that, on average, while saline did not cause any significant change in respiratory mechanics, a low dose (0.4 mg) of inhaled fenoterol was followed by a rapid (5 min) and significant decrease in Rrs_{max} (−33%), Rrs_{min} (−28%), EELV (−34%), and $PEEP_i$ (−44%), with a slight but not significant further fall with higher doses. However, changes were short-lasting, and by 2 h after the end of administration were no longer significant. PaO_2 dropped significantly on average, with a maximum mean fall of 15 mmHg. We conclude that low doses of aerosolized fenoterol have a powerful and rapid but short-acting bronchodilating effect in mechanically ventilated patients with chronic airflow obstruction, bringing about a marked decrease in the dynamic pulmonary hyperinflation. These changes in respiratory mechanics can be easily and safely measured at the patient's bedside.

Key words: Chronic airflow obstruction (CAO) – Acute respiratory failure – Mechanical ventilation – Respiratory mechanics – Intrinsic PEEP – Pulmonary hyperinflation – Bronchodilators – Adrenergic agonists

Adrenergic agents are widely used in the therapy of acute [1, 2] and chronic airflow obstruction (CAO) [3]. Gay and colleagues [4] have recently shown that in mechanically ventilated patients with acute respiratory failure (ARF), metaproterenol, a selective β_2-sympathomimetic agent, can bring about significant bronchodilatation, thereby reducing dynamic pulmonary hyperinflation and intrinsic positive end-expiratory pressure ($PEEP_i$) [5]. These changes in respiratory mechanics are important, since they can improve the patient-ventilator interaction, e. g., during triggered machine cycles (assisted mechanical ventilation or pressure support [6]), as well as provide a needed background for weaning [7, 8]. However, Gay and his colleagues did not investigate either the dose-response relationship or the time course of bronchodilatation and did not measure changes in the arterial oxygen tension (PaO_2), although sympathomimetic agents might exaggerate preexisting ventilation–perfusion inequalities and cause a fall in PaO_2 [9].

Since this kind of information is available regarding asthmatics and patients with stable CAO, but not critically ill patients, we undertook this study to investigate the dose-response relationship and the time course of the effect of an inhaled β_2-adrenergic agonist, fenoterol [10], on respiratory mechanics and arterial oxygen tension in mechanically ventilated patients with ARF due to acute exacerbation of CAO.

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Patients and methods

Seven consecutive critically ill patients (two men and five women, mean age ±SD 67.6±5.7 years), who needed ventilatory support in the intensive care unit due to severe acute exacerbation of CAO, were recruited for this study and were examined within 3 days of the instigation of mechanical ventilation.

The investigative protocol was approved by the institutional ethics authorities and informed consent was obtained from the patients or from their next of kin.

In all our patients, CAO was due to chronic bronchitis or emphysema; no patient had a preexisting diagnosis of asthma. All patients were intubated (Portex cuffed endotracheal tube, internal diameters 7.5–8.5 mm) and under controlled mechanical ventilation using the 100% intermittent mandatory ventilation mode of the Servo 900C Siemens ventilator with constant inspiratory flow ($\dot{V}_I$). Patients were ventilated without PEEP and were sedated with benzodiazepine. The adjustment of the mechanical ventilation and the need for sedation were determined by the primary physicians according to their clinical judgment. No patient was sedated because of our study, and no change was made in the settings of the ventilation equipment during the study. The ventilatory pattern and the arterial blood gases as measured at the time of the study are presented in Table 1. The pharmacotherapy (steroid, mucolytic agents, etc.) had been prescribed by the attending physicians in the hours or days preceding the study and was left unaltered throughout the procedure. All seven patients were receiving aminophylline infused at a constant rate (0.5–0.7 mg/kg h) and three of them were receiving steroids (methylprednisolone, 60 mg/day) at the time of the study, but no patient received adrenergic agonists, either intravenously or by inhalation, after admission into the intensive care unit 12 h or more before this study – though sympathomimetics had probably been generally used during the stay in the medical wards. We therefore feel confident that our patients were not under the effect of sympathomimetic bronchodilators when they were examined.

Table 1. Ventilatory pattern and blood gases

	VT (L)	f (breaths/min)	TI/TE	$\dot{V}I$ (l/s)	FiO_2	PaO_2 (mmHg)	$PaCO_2$ (mmHg)	pH
Mean	0.80	12.2	1:2.4	0.79	0.39	105.0	38.2	7.44
SD	±0.09	±0.4	±0.09	±0.09	±27.6	±6.7	±0.05	

VT, tidal volume; f, breathing frequency; TI/TE, inspiratory to expiratory time ratio; $\dot{V}I$, constant inspiratory flow

Airway pressure (P_{aw}) and flow ($\dot{V}$) were measured with the pressure transducers incorporated into the Servo 900C; expired lung volume (VT) was obtained by electrical integration of the flow signal [11]. All signals were calibrated independently and recorded on a multichannel pen recorder (Mingograph, Siemens), at a paper speed of 15.5 or 31 mm/s. Arterial blood gases were measured with an IL 1302 (Instrumentation Laboratories).

Procedure and data analysis

Patients were examined in the semirecumbent position, and a physician not involved in the experimental procedure was always present to attend them. After regular mechanical ventilation (with the patient relaxed) had been recorded for several breaths, the airway opening was occluded at the end of a tidal expiration, using the end-expiratory hold button of the ventilator, for direct measurement of "intrinsic" PEEP [5, 12]. The occlusion was then released for the mechanical lung inflation, and the airway opening was occluded again at the end of the inflation by means of the end-inspiratory hold button of the ventilator. After the occlusion there was an immediate drop in P_{aw} from its maximum value (P_{max}) to a lower value (P_1), followed by a gradual decrease until an apparent plateau (P_2)was reached [13]. P_2 thus represented the elastic recoil pressure of the total respiratory system at the end of the mechanical inflation. After the P_{aw} plateau was seen (about 1.5–2 s), the occlusion was released and expiration allowed to the elastic equilibrium volume, i.e., until the expiratory flow became nil. In all patients complete expiration went well below the end-expiratory lung volume (EELV) during regular mechanical ventilation. The EELV was computed from the difference between the end-tidal volume and the elastic equilibrium volume.

The static compliance of the total respiratory system (Cst_{rs} was computed by dividing the expired tidal volume (VT) by the difference between the end-inspiratory and the end-expiratory plateau pressure [5]. Cst_{rs} was corrected for the compliance of the ventilator tubings and gas compression, which amounted to 0.7 ml/cmH_2O in the range of the experimental volume and flow.

The resistive properties of the total respiratory system were obtained as previously described [13]. Briefly, the "true" (i.e., ohmic) resistance of the respiratory system (minimum intrinsic respiratory resistance, Rrs_{min}) was calculated by dividing the immediate drop in pressure following the end-inspiratory occlusion ($P_{max}-P_1$) by the preceding constant flow and subtracting the resistance of the endotracheal tube and inspiratory line of the ventilator. By dividing $P_{max}-P_2$ by the preceding constant flow and again subtracting the resistance of the endotracheal tube and inspiratory line of the ventilator, maximum intrinsic respiratory resistance (Rrs_{max}) was calculated. The latter includes Rrs_{min} plus the "additional" inspiratory dynamic impedance resulting from time-constant inequalities within the lungs and chest wall and/or stress relaxation. Rrs_{min} should correspond to the resistance at high frequency, whereas Rrs_{max} reflects the resistance at very low frequency (i.e., near zero) [14–16]. The resistance of the endotracheal tube was ascertained as previously described [13]. The resistance of the inspiratory line of the ventilator was computed in each study by measuring the pressure and flow while the patient was disconnected for a few breaths from the ventilator. The circuit resistance was flow-dependent, but did not change appreciably within the range of volume in this study. We also corrected Rrs for the finite occlusion time of the occlusion valve of the Servo 900C according to the technical observations of Kochi and colleagues [17].

Saline solution and drug were administered by means of a small-volume aerosol generator (Servo Nebulizer 945, Siemens-Elema, Stockholm, Sweden) attached to the inspiratory gas source at one end and to a nebulizing chamber (Cirrus Mark II Nebulizer, Malvern Instruments, Malvern, England) at the other end. Minute ventilation was corrected for the extra volume delivered by the nebulizer, such that it did not change throughout the procedure. The nebulizing chamber required a minimum of 6.5 l/min to obtain an output of 2 ml in less than 6 min. We regulated the nebulizer to obtain an output of 4 ml in 10 min. The average particle size range of the nebulizing chamber is 2–5 μm; the aerodynamic mass mean diameter is 7.19 and 6.19 μm at a flow of 6 and 8 l/min respectively (personal communication from Siemens-Elema).

After baseline measurements of respiratory mechanics and PaO_2 were performed, 4 ml saline aerosol was administered by the nebulizer-ampulla system in 10 min and measurements were performed again 5, 10, and 30 min after the end of the administration. Then fenoterol (0.1% solution) was administered also by aerosol in a cumulative dose-response fashion in three steps, at 0.4, 0.8, and 1.2 mg, each dose being delivered over 10 min. The doses were obtained by diluting the original 0.1% solution appropriately (e.g., 0.4 mg was administered in 10 min by 4 ml of a 0.0001% solution). Respiratory mechanics and PaO_2 were measured at 5, 15, and 30 min (PaO_2 only at 30 min) after each dose and at 60, 120, and 180 min after the last dose.

All data are presented as the mean ± SD. The Friedman nonparametric two-way analysis of variance for repeated measurements was used to evaluate groups of data. Then differences between control values and those after administration of saline and fenoterol were tested using Wilcoxon's rank test for paired data. The criterion of significance was taken as $p<0.05$.

Results

The results (mean ± SD) of respiratory mechanics under control conditions and after inhalation of saline and of

Table 2. Respiratory mechanics and arterial oxygen tension

	P_{max} (cmH_2O)	Cst_{rs} (l/cmH_2O)	Rrs_{max} ($cmH_2O/l \cdot s^{-1}$)	Rrs_{min} ($cmH_2O/l \cdot s^{-1}$)	EELV (l)	$PEEP_i$ (cmH_2O)	PaO_2 (mmHg)
Control							
	46.5	0.052	18.1	9.5	0.27	5.9	105.0
	±2.2	±0.007	±6.4	±5.4	±0.24	±3.9	±27.6
Saline							
	46.2	0.052	18.1	9.6	0.27	5.9	104.0
	±2.4	±0.007	±6.2	±5.2	±0.24	±3.8	±27.1
Fenoterol							
Dose 0.4	41.1*	0.048	13.0*	6.4*	0.19*	3.3*	94.1*
	±2.8	±0.007	±3.3	±3.1	±0.24	±3.0	±15.3
0.8	40.3*	0.051	12.6*	6.3*	0.15*	2.6*	90.1*
	±3.1	±0.009	±4.0	±3.6	±0.20	±2.5	±15.6
1.2	39.4*	0.052	11.4*	5.4*	0.11*	2.6*	97.6*
	±4.2	±0.009	±4.0	±3.6	±0.10	±2.4	±18.6
Time 60 min	41.4*	0.054	13.0*	6.0*	0.24	4.1	97.0
	±2.5	±0.010	±2.7	±2.2	±0.28	±3.7	±23.1
120 min	42.6	0.055	14.3	7.1	0.26	4.2	99.3
	±2.8	±0.011	±2.6	±2.8	±0.31	±3.8	±22.0
180 min	44.1	0.054	15.1	7.8	0.26	4.9	103.1
	±3.8	±0.013	±3.1	±3.6	±0.31	±3.9	±33.2

P_{max}, peak inspiratory airway pressure; Cst_{rs}, static respiratory compliance; Rrs_{max} and Rrs_{min}, maximum and minimum respiratory resistance after subtraction of the resistance of the endotracheal tubes and the inspiratory line of the ventilator; EELV, end-expiratory lung volume; $PEEP_i$, intrinsic positive end-expiratory pressure.

Mean values after each dose pertain to measurements after 30 min, since there was no significant difference between the 5-, 15-, and 30-min measurements. PaO_2 was measured only 30 min after each dose. ANOVA was significant for P_{max}, Rrs_{max}, Rrs_{min}, EELV, $PEEP_i$ and PaO_2 ($p<0.05$); then, all values were compared to control values using the Wilcoxon's test for paired data. *, $p<0.05$

fenoterol are reproduced in Table 2. Since we did not find any significant difference between measurements taken at 5, 15, and 30 min after the administration of each dose, we have presented in this table only the measurements taken at 30 min.

Under control conditions, all these CAO patients showed dynamic pulmonary hyperinflation. The end-expiratory tidal volume ranged between 0.08 and 0.8 l above the elastic equilibrium volume, and the end-expiratory alveolar pressure, i.e. $PEEP_i$, ranged between 2 and 12 cmH_2O. Baseline Cst_{rs} was slightly lower than normal [18], probably reflecting pulmonary hyperinflation [5]. Respiratory resistance was higher than normal in all patients. Normal values for Rrs_{max} have been provided by Don and Robson [19], who obtained a mean value of 4.8 cmH_2O/l s in supine anesthetized subjects using a method similar to the present one. To our knowledge, values of Rrs_{min} in normal subjects have not yet been reported. However, it must be noted that in our patients not only was Rrs_{max} much higher than the normal values provided by Don and Robson, but Rrs_{min} was also on average almost twice as high as normal Rrs_{max} (Table 2).

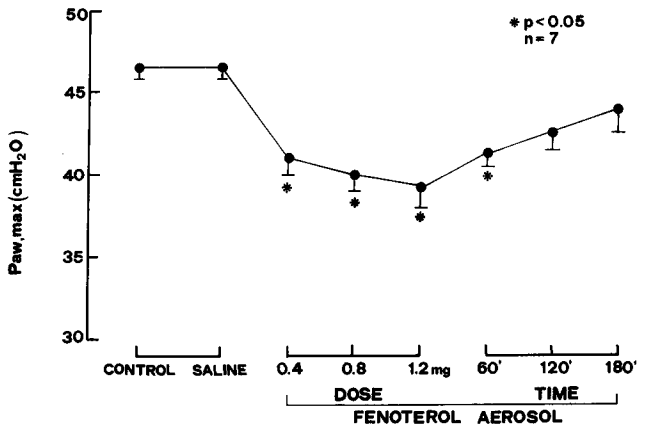

Fig. 1. Effect of fenoterol on maximum airway pressure (P_{max}) with increasing doses (0.4, 0.8, and 1.2 mg) and 60, 120, and 180 min after the last, highest dose. *Filled circles* show mean values from seven patients, and bars the standard error. Since mean values did not change significantly between 5 min and 30 min after each dose, values presented in the figure are those from measurements at 30 min. Analysis of variance (ANOVA) was significant ($p<0.05$). All values are compared to control values using Wilcoxon's test for paired data. *, $p<0.05$

After inhalation of saline no variable of respiratory mechanics changed significantly. By contrast, inhalation of fenoterol brought rapid and sharp, although not longlasting, changes in respiratory mechanics (Table 2).

On average, P_{max} (Fig. 1) dropped significantly below the control value following the first dose (0.4 mg, −12%, $p<0.05$) and the last dose (1.2 mg, −15%, $p<0.05$) of fenoterol. The mean decrease was still −11% ($p<0.05$) at 60 min after the last dose, but was only −5% at 180 min after (not significant). The lower P_{max} was mainly due to the significant fall in respiratory resistance, both Rrs_{max} and Rrs_{min} (Fig. 2), which decreased the resistive component of P_{aw}; Cst_{rs}, the elastic component, did not, on average, change significantly throughout the study (Fig. 3). Five minutes after administration of 0.4 mg fenoterol Rrs_{max} and Rrs_{min} were on average 28% and 33%, respectively lower than control, with a slight but not signifi-

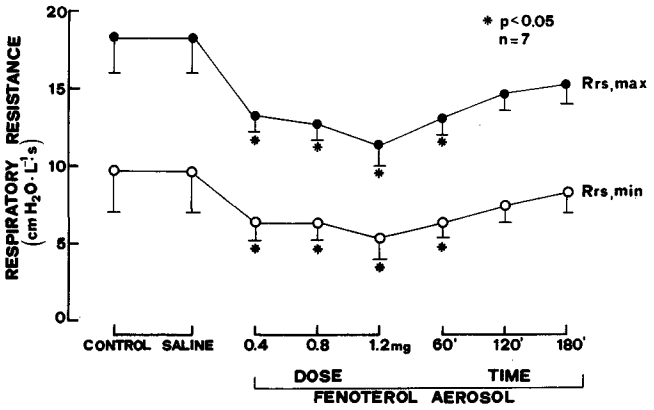

Fig. 2. Effect of fenoterol on maximum and minimum respiratory resistance (Rrs_{max} and Rrs_{min}, respectively). Resistance of the endotracheal tubes and ventilator devices has been subtracted from the total. ANOVA was significant ($p<0.05$). All values are compared to control values using Wilcoxon's test for paired data. *, $p<0.05$. (Symbols as in Fig. 1)

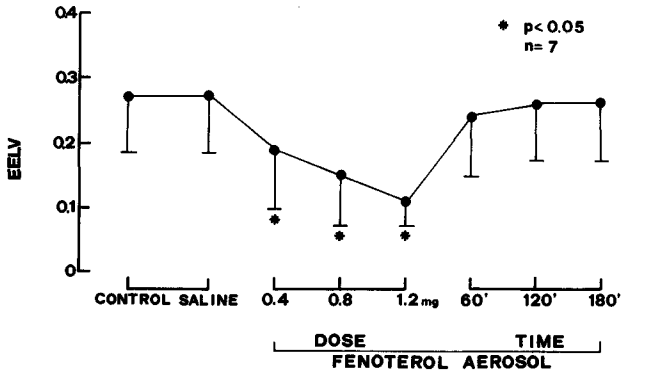

Fig. 4. Effect of fenoterol on the end-expiratory lung volume (EELV), computed as the difference between the end-tidal volume and the elastic equilibrium volume reached during a complete relaxed expiration. ANOVA was significant ($p<0.05$). Values are compared to control values using Wilcoxon's test for paired data. *, $p<0.05$. (Symbols as in Fig. 1)

cant further decrease as doses increased. Two hours after inhalation of the last dose, both Rrs_{max} and Rrs_{min} were slightly but no longer significantly lower than control, and were again approaching the initial value by the 180-min measurement (Fig. 2).

The faster tidal expiration due to lower airflow resistance significantly reduced the EELV (Fig. 4), which ranged between 0.04 and 0.2 l above the equilibrium volume after the highest dose of fenoterol (40% of the control value, on average). $PEEP_i$ was also markedly lowered to 56% and 44% of the control value by 0.4 and 1.2 mg inhaled fenoterol, respectively (Fig. 5). However, neither EELV nor $PEEP_i$ was significantly different from the control value 60 min after the last administration of fenoterol.

The data have been presented as mean ±SD in order to provide an immediate overview of the study, and, although there was some variation between patients and between parameters, it was not large, so changes in the mean well represent changes in the effect of fenoterol in our patients in regard to dose response and time course. However, some of the individual differences should be pointed out, since this could prompt a more individual therapeutic approach. For example, in two patients both Rrs_{max} and Rrs_{min} and also $PEEP_i$ dropped by a further 20% and 50% respectively after 1.2 mg fenoterol, following the initial slight drop after 0.4 mg. This indicates that, at least in some CAO patients, increasing doses of fenoterol may potentiate the bronchodilating effect. In another patient Rrs_{min} did not change and Rrs_{max} decreased by 13% with 0.4 mg fenoterol, while $PEEP_i$ decreased by 50%, indicating that, sometimes, small changes in respiratory resistance suffice to reduce the dynamic pulmonary hyperinflation significantly.

Figure 6 shows that inhalation of fenoterol brought about a slight but significant decrease in the arterial oxygen tension. In fact, PaO_2 at its minimum (after 0.8 mg fenoterol) was on average 15 mmHg lower than the control value, approaching the control value again at the 120-min measurement. However, it has to be noted that PaO_2 ranged between values which did not challenge hemoglobin oxygen saturation, since it was at all times above 60 mmHg. No significant change was observed in $PaCO_2$. No patient suffered any significant side effects

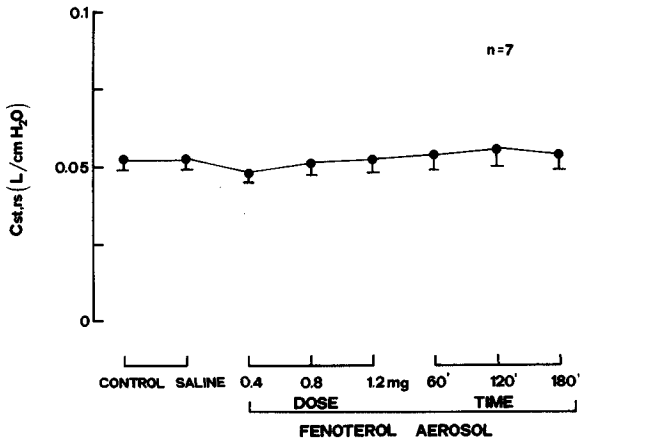

Fig. 3. Effect of fenoterol on static respiratory compliance (Cst_{rs}). ANOVA was not significant ($p>0.05$). (Symbols as in Fig. 1)

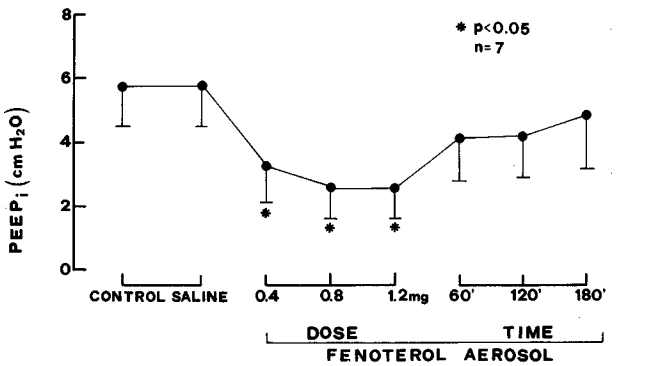

Fig. 5. Effect of fenoterol on intrinsic positive end-expiratory pressure ($PEEP_i$), i.e., the end-expiratory recoil pressure of the respiratory system measured by means of the end-expiratory tidal occlusion. ANOVA was significant ($p<0.05$). All values are compared to control values using Wilcoxon's test for paired data. *, $p<0.05$. (Symbols as in Fig. 1)

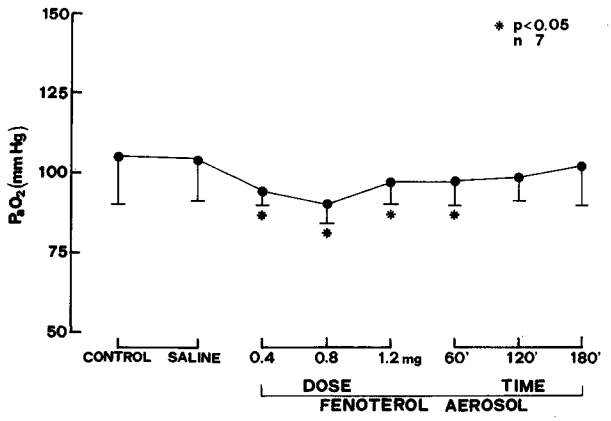

Fig. 6. Effect of fenoterol on arterial oxygen tension (PaO_2). Measurements were performed 30 min after each dose. ANOVA was significant ($p<0.05$). Values are compared to control values using Wilcoxon's test for paired data. (Symbols as in Fig. 1)

(cardiac arrythmias, systemic arterial hypertension) throughout the study.

Discussion

Four conclusions can be drawn from the results of this study.

1. Fenoterol, a selective β_2-adrenergic agonist, administered by inhalation, effected significant bronchodilatation and reduced dynamic pulmonary hyperinflation in mechanically ventilated patients with CAO. There was also a slight but significant reduction in the arterial oxygen tension.
2. These effects were rapid, since they were already present 5 min after the end of inhalation and were obtained at low doses of the drug (0.4 mg) without further important improvement at higher doses, at least as administered and at the doses used in this study.
3. Changes in respiratory function were not longlasting, since no variable was significantly different from the control value 2–3 h after the end of drug administration.
4. The effects of drugs on respiratory mechanics in mechanically ventilated patients can be easily assessed by noninvasive measurements made at the bedside.

The lack of changes in respiratory mechanics after inhalation of saline solution strongly supports the conclusion that the marked decrease in respiratory resistance and dynamic pulmonary hyperinflation (lower EELV and $PEEP_i$) were determined by the pharmacological action of fenoterol. Because all our patients with CAO were receiving aminophylline at the time of the study, the bronchodilating effect of fenoterol should be considered as additional to the action of aminophylline, which is known to share the effect of adrenergic stimulants on bronchial smooth muscle relaxation [20, 21].

These changes in respiratory mechanics – i.e., lower respiratory resistance and lower $PEEP_i$ and lung volumes – are important in mechanically ventilated CAO patients with ARF. During controlled mechanical ventilation, the reduced $PEEP_i$ (45% of the control value, at its lowest) decreases the possible adverse effects of high end-expiratory alveolar pressure (e.g., decreased cardiac output or barotrauma) [12]. With ventilatory modes requiring the patient's cooperation, e.g., assisted mechanical ventilation and pressure support, the work of breathing done by the patient is not negligible, as shown by Marini and colleagues [22]. The fall in resistance effected by fenoterol decreases the resistive component of the work of breathing and therefore the mechanical load on the respiratory muscles of a patient participating in inspiration. Furthermore, the reduced $PEEP_i$ decreases the ventilatory load for the patient's inspiratory effort. In fact, although the negative "triggering" pressure is commonly set at a few cmH_2O, this is on top of $PEEP_i$, i.e., the end-expiratory elastic recoil which has to be counterbalanced in order to initiate the breath, so that the magnitude of the total negative pressure ($PEEP_i$ plus the triggering pressure) which has to be created by the inspiratory muscles is not negligible [7]. In addition, the decreae in lung volume, because of the faster expiration, improves the mechanical efficiency of the inspiratory muscles because of their force length characteristics [23]. This should be important also for the weaning of patients with CAO. However, in our study, the beneficial effect of fenoterol was short-lasting, so its actual efficiency on the process of weaning CAO patients needs further investigation.

The amount of dynamic pulmonary hyperinflation, i.e., EELV and $PEEP_i$ values, in the CAO patients in this study was much lower than that reported elsewhere in CAO patients examined on the 1st day of mechanical ventilation [24, 25], which probably reflects the effects of therapy in the days preceding our study as well as the fact that our patients were receiving aminophylline at the time of the study.

The rapidity of action of fenoterol in our patients (in most instances a maximum or nearly maximum effect was evident 5 min after inhalation of 0.4 mg fenoterol), suggests that, among the several effects of β_2-stimulants which have been proposed to be of therapeutical importance, bronchial smooth muscle relaxation is the most relevant in mechanically ventilated patients, even when the etiology of the CAO is chronic bronchitis or emphysema and not asthma [20]. In fact, according to the analysis by Bates and colleagues [14], changes in Rrs_{min} are mainly determined by changes in the airway caliber, whereas Rrs_{max} includes Rrs_{min} and the additional impedance of the periphery of the lung (i.e., stress relaxation and time-constant inequalities). Figure 2 shows that both Rrs_{min} and Rrs_{max} decreased following inhalation of fenoterol, and Rrs_{max} decreased mainly because of the lower Rrs_{min}. However, the difference between Rrs_{max} and Rrs_{min} also decreased slightly (on average from 8.5 ± 2.6 to 6.6 ± 1.9 cmH_2O/l s; $p<0.05$), indicating that fenoterol was slightly active on the peripheral impedance of the lung.

Compared to the results obtained in many asthmatic patients, the effect of fenoterol in our mechanically ventilated CAO patients was shorter and less dose-related [10, 20]. In asthmatics, in fact, the peak effect was observed between 30 and 60 min, with a duration up to 6–8 h and FEV_1 increased with increasing dosage up to 2.4 mg. We did not use doses higher than 1.2 mg and therefore we

cannot exclude the possibility that higher doses (e.g., 2.4 mg) may have a more powerful effect. However, we did not observe any mean significant change in the respiratory function when the dose of inhaled fenoterol was increased from 0.4 to 1.2 mg. This difference between our results and those of other authors [10, 20] could be due in part to differences as to underlying airway and lung pathology and aerosol distribution in asthmatics and in acutely ill CAO patients, not only within the lung, but also in regard to the presence of the endotracheal tube. Moreover, we do not know whether the particle size of the aerosol generator used in this study allowed an uniform distribution of the drug. The differences to other results reported in non-intubated patients [10, 20] might also be due to the fact that our patients were examined while receiving aminophylline, and therefore their response to adrenergic stimulation had been in part offset by bronchodilatation caused by the aminophylline, such that the maximum relaxant effect had been reached. It is probably a good therapeutic choice to combine β_2-receptor agonists with aminophylline infusion in order to achieve maximum bronchial smooth muscle relaxation. The option also exists of decreasing the dosage of aminophylline by increasing that of the β_2-receptor agonists, in order to minimize the side effects of methylxanthines. Existing data on stable CAO patients and asthmatics would support the supposition that the bronchodilating action of β_2-adrenergic agonists is superior to that of methylxanthines. However, we have observed that doxofylline (a new methylxanthine) can bring about efficient bronchodilatation in CAO patients in intensive care [26].

Another possible explanation of the differences in the time-course and dose-related effects might be development of tolerance to adrenergic stimulation [20]. It is very likely, in fact, that our patients had been treated with bronchodilators for the period preceding the development of ARF, and they might be considered at risk of having developed tachyphylaxis. However, although this problem has been widely discussed since reports in the late 1960s [27] and is supported by the evidence of several studies, it was never shown to be of clinical importance. Three of our patients with CAO were receiving steroids (see methods) when we examined them. Steroids are known to reestablish the response to β_2-agonists, but the effect of fenoterol on resistance and $PEEP_i$ in these patients was not different from that in the four patients not receiving steroids.

In their study on the effect of metaproterenol, Gay and colleagues [4] suggested that quick and simple assessment of the efficiency of bronchodilatation in mechanically ventilated patients can be obtained in the clinical setting by measurements of changes in $PEEP_i$ and P_{max}. In fact, measurement of $PEEP_i$ allows quantification of changes in dynamic pulmonary hyperinflation and in the "inspiratory threshold load", both of which could be important variables for successful weaning [8]. By contrast, P_{max} is a rough measurement of respiratory function, since it includes both the resistive and the elastic components of airway pressure [14], such that, in some patients, changes in compliance can offset changes in resistance [26]. The end-expiratory and end-inspiratory occlusions can be performed within a few seconds without any discomfort to the patient, in two consecutive breaths, and values of $PEEP_i$, resistance (both maximum and minimum), and compliance (corrected for $PEEP_i$) could be provided "online" by modern computer-equipped ventilators, for better individualized evaluation.

We found that inhalation of fenoterol effected a significant drop in the arterial oxygen tension, although values of PaO_2 were always high enough to save hemoglobin oxygen saturation. Several mechanisms have been invoked to explain the effect of inhaled sympathomimetic agents on PaO_2, for example, reversal of hypoxemia-induced pulmonary vasoconstriction in poorly ventilated airspaces, or increase in cardiac output with excessive perfusion of hypoventilated alveoli [28]. This effect can be easily controlled with oxygen administration but must be considered when β-receptor agonists are administered to critically ill patients who can be hypoxemic without adequate oxygen supply.

In summary, we conclude that fenoterol is a rapid, powerful, but short-acting bronchodilator in mechanically ventilated, nonasthmatic patients with ARF due to severe exacerbation of CAO. It is safe, at least at the doses used in this study, but can reduce arterial oxygen tension, and it is therefore suggested that oxygen be supplied during the treatment. The efficiency and the time course of the bronchodilatation in each patient can easily be assessed at the bedside by detailed noninvasive measurements of the respiratory mechanics.

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