Effects of inhaled fenoterol and positive end-expiratory pressure on the respiratory mechanics of patients with chronic obstructive pulmonary disease

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BACKGROUND: During acute ventilatory failure in patients with chronic obstructive pulmonary disease (COPD), applying external positive end-expiratory pressure (PEEP) will reopen small airways and, thus, may enhance peripheral deposition as well as the physiological effects of inhaled beta-2 agonists.

OBJECTIVE: To investigate the efficacy of inhaled fenoterol applied by zero end-expiratory pressure (ZEEPe) or PEEPe.

METHODS: Ten patients with COPD who were intubated and mechanically ventilated received fenoterol (10 mg/4 mL) via the ventilator using a jet nebulizer for 30 min on ZEEPe and PEEPe set at 80% of the total PEEP in a random order. The total resistance of the respiratory system (rapid airway occlusion technique), change in end-expiratory lung volume and expiratory flow limitation were assessed before and 5 min, 15 min, 30 min, 60 min and 240 min after fenoterol inhalation.

RESULTS: Before inhalation and 60 min after inhalation, the total PEEP, the change in end-expiratory lung volume and the total resistance of the respiratory system were 8±3 cmH2O and 6±3 cmH2O, 0.61±0.34 L and 0.43±0.32 L, and 26±7 cmH2O/L/s and 23±6 cmH2O/L/s, respectively, with ZEEPe, and 9±3 cmH2O and 8±3 cmH2O (P<0.05 versus ZEEPe), 0.62±0.34 L and 0.62±0.37 L (P<0.05 versus ZEEPe), and 26±9 H2O/L/s and 25±9 H2O/L/s, respectively, with PEEPe. Three patients became not flow-limited under the combination of ZEEPe and fenoterol.

CONCLUSIONS: In patients with COPD, fenoterol combined with PEEPe has opposing effects on respiratory mechanics. First, it does not significantly reduce lung hyperinflation or inspiratory resistances. Second, it allows expiratory flow limitation reversal in some patients. These findings result from the net effect on end-expiratory lung volume of each intervention. This implies that if fenoterol is used in combination with PEEPe, the level of PEEPe should be reassessed during the time course of the drug to prevent any further lung hyperinflation.

Key Words: Chronic obstructive pulmonary disease; Expiratory flow limitation; Inhaled beta-2 agonist; Resistance of the respiratory system; Respiratory mechanics

Les effets du fenotérol en aérosol et de la pression positive en fin d’expiration sur la mécanique respiratoire de patients atteints d’une maladie pulmonaire obstructive chronique

HISTORIQUE: Pendant l’échec ventilatoire aigu de patients atteints d’une maladie pulmonaire obstructive chronique (MPOC), l’application de pression positive en fin d’expiration externe (PFEe) rouvre les petites voies respiratoires et peut donc améliorer les dépôts périphériques et les effets physiologiques des béta-agonistes en aérosol.

OBJECTIF: Explorer l’efficacité du fenotérol en aérosol appliquée par pression nulle en fin d’expiration (PNFEe) ou par PFEe.

MÉTHODOLOGIE: Dix patients atteints de MPOC intubés et sous ventilation mécanique ont reçu du fenotérol (10 mg/4 mL) par le ventilateur, au moyen d’un nébuliseur à pression pendant 30 minutes par PNFEe et par PFEe, fixée à 80 % de la PFEe totale selon un ordre aléatoire. La résistance totale du système respiratoire (technique d’occlusion rapide des voies respiratoires), les modifications du volume pulmonaire en fin d’expiration et les limites du débit respiratoire ont été évaluées avant l’inhalation de fenotérol et 5 min, 15 min, 30 min, 60 min et 240 min après cette inhalation.

RÉSULTATS: Avant l’inhalation et 60 minutes après, la PFEe totale, la modification du volume pulmonaire en fin d’expiration et la résistance totale du système respiratoire s’élevaient à 8±3 cmH2O et à 6±3 cmH2O, 0.61±0.34 L et à 0.43±0.32 L et à 26±7 cmH2O/L/s et à 23±6 cmH2O/L/s respectivement, avec PNFEe, et à 9±3 cmH2O et à 8±3 cmH2O (P<0.05 par rapport à PNFEe), 0.62±0.34 L et à 0.62±0.37 L (P<0.05 par rapport à PNFEe), et à 26±9 H2O/L/s et à 25±9 H2O/L/s respectivement, avec PFEe. Les débits de ces patients n’étaient pas limités avec l’association de PNFEe et de fenotérol.

CONCLUSIONS: Chez les patients atteints d’une MPOC, le fenotérol associé à une PFEe avait des effets antagonistes sur la mécanique respiratoire. D’abord, il ne réduit pas de manière significative l’hyperinflation pulmonaire ou les résistances inspiratoires. Ensuite, il permet de renverser les limites du débit respiratoire chez certains patients. Ces observations décodent de l’effet net de chaque intervention sur le volume pulmonaire en fin d’expiration. Cette constatation sous-tend que si du fenotérol est utilisé en association avec la PFEe, le taux de PFEe devrait être réévalué pendant la durée d’administration du médicament afin de prévenir une augmentation de l’hyperinflation pulmonaire.
Reducing the load imposed on the respiratory system is a major goal in the management of patients with chronic obstructive pulmonary disease (COPD) during acute ventilatory failure (AVF) (1). This task can be achieved by short-acting beta-2 (\( \beta_2 \)) agonists (2-4). Although in vitro studies (5,6) have demonstrated that the delivery of \( \beta_2 \) agonists can be improved by adjusting ventilatory settings, a series of clinical studies (7-10) have failed to demonstrate that changing ventilatory settings can improve the efficacy of inhaled \( \beta_2 \) agonists in intubated and mechanically ventilated patients with COPD.

Adding external positive end-expiratory pressure (PEEP\(_{e} \)) to mechanical ventilation can reduce the work of breathing by offsetting the elastic load represented by intrinsic PEEP (PEEP\(_{i} \)) (11-13). To avoid the risk of hemodynamic worsening or volutrauma, the amount of PEEP\(_{e} \) should not exceed 80% to 85% of the PEEP\(_{i} \) (14). According to the ‘waterfall theory’ (15), this is valid in cases of expiratory flow limitation. In the absence of expiratory flow limitation, airway opening pressure is transmitted to the lung through open (not collapsed) small airways that PEEPe may be able to reopen small airways during the breathing cycle (16). By maintaining the patency of small airways plays a critical role in patients with COPD who are mechanically ventilated for AVF, and it has been suggested that PEEPe may be able to reopen small airways during the breathing cycle (16). By maintaining the patency of small airways and evening lung inflation. The closure of transmited to the lung through open (not collapsed) small airways plays a critical role in patients with COPD who were intubated and mechanically ventilated patients with COPD.

**METHODS**

Patients were investigated in a semirecumbent position and received a continuous intravenous infusion of midazolam (0.10 mg/kg) as part of routine therapy. If necessary, atracurium (0.3 mg/kg to 0.6 mg/kg) was used to ensure full relaxation during measurements.

**Equipment**

The pressure at the airway opening (Pao) was measured from a port proximally located to the endotracheal tube and connected to a pressure transducer (DP 55±100 cmH\(_2\)O, Validyne, USA) via a rigid polyethylene tube (1.7 mm internal diameter). Air flow (V\(_{V} \)) was measured by a pneumotachograph (3700 A, Hans Rudolph, USA) inserted between the port of Pao and the Y-piece of the ventilator circuit. The pressure drop across the two ports of the pneumotachograph was measured with a differential pressure transducer (DP 55±5 cmH\(_2\)O, Validyne). The pneumotachograph was linear over the experimental range of V\(_{V} \) (±2.5 L/s).

Changes in lung volume were measured by numerical integration of the V\(_{V} \) signal. V\(_{V} \), volume and Pao signals were amplified (AC Bridge Amplifier – ABC module, Raytech Instruments, Canada), low-pass filtered at 50 Hz, sent to a 16-bit analog-to-digital converter (Direc Physiologic Recording System, Raytech Instruments) and sampled at 200 Hz. Digitized signals were continuously displayed on a computer screen with respect to time, and also as V\(_{V} \)-volume loops. Recordings were stored for further analysis (Anadat-Labdat 5.1, RHT-InfoDat Inc, Canada). Transducers were calibrated before each experiment. Equipment dead space was 100 mL. Standard low-compliance ventilator tubing was used and the humidifier was turned off during drug delivery and measurements.

The device used to assess expiratory flow limitation by the negative expiratory pressure technique (21) was attached between the Y-piece of the ventilatory circuit and the pneumotachograph. Once manually activated, it delivered a negative pressure of –5 cmH\(_2\)O during tidal expiration from an expiratory flow of 30 mL/s. Both the measurement setup and the negative expiratory pressure device were removed during drug administration and reinstalled later at the time of measurement.

**Drug delivery**

A jet small-volume nebulizer (NL9, DTF, France) was filled with 10 mg fenoterol in 4 mL solution. The nebulizer was attached to the inspiratory line 20 cm upstream of the Y-piece of the ventilatory circuit. The ventilator was equipped with a nebulization function which allowed it to deliver the nebulization synchronously with inflation. Once this procedure was activated, part of the inspiratory flow was diverted to feed the nebulizer at a flow rate of 6 L/min. During the 30 min nebulization period, the baseline ventilatory settings remained constant (Table 1). From previous in vitro studies at these settings, the median mass aerodynamic diameter was known to be 2 µm to 3 µm (unpublished results). Fenoterol was delivered during mechanical ventilation at ZEEPe, and PEEPe was set at 80% of total PEEP obtained after end-expiratory occlusion on ZEEPe. The PEEPe level was randomly assigned to each
Changes in end-expiratory lung volume (FRC) was determined using the negative expiratory pressure test (23). Expiratory flow limitation was assessed by inspiratory occlusion. End-inspiratory occlusion was performed manually using the ventilator controls. Expiratory flow limitation was quantified in terms of the extent of expiratory flow limitation was measured as the plateau pressure in Pao obtained 3 s after the end-inspiratory rapid airway occlusion technique as previously described (22). Briefly, after end-inspiratory occlusion, Pao went down from a maximal value (Pao,max) to P1, which is the value of Pao at the first zero V'. This was followed by a slow decay to an apparent plateau pressure (Pao,plat) within several seconds of occlusion. The value of Pao,plat was taken 5 s after the end-inspiratory occlusion. End-inspiratory occlusion was performed manually using the ventilator controls. Expiratory flow limitation was determined using the negative expiratory pressure test (23).

Changes in end-expiratory lung volume (ΔFRC) between tidal expiration and relaxation volume of the respiratory system (Vr) were obtained as previously described (4). Briefly, the ventilator frequency was reduced to its lowest value during the baseline cycle (while removing PEEPi if present), thus prolonging the expiratory duration to allow the patient to exhale to Vr. Vr was achieved when expiratory flow became nil and end-expiratory occlusion resulted in no change in airway pressure (ie, no PEEPi). The measurements were performed before and 5 min, 15 min, 30 min, 60 min and 240 min after the end of fenoterol administration at each PEEPi level.

### Data analysis

A consecutive pair of V'-volume loops, one immediately before (control) and the other during the application of negative expiratory pressure were superimposed and compared (21,24). If expiratory flow with negative expiratory pressure was higher than it was under the control condition, then the patient was classified as being flow-limited. If the negative expiratory pressure (all or part of the expiratory V'-volume curve) overlapped with the control curve, then the patient was classified as flow-limited. The extent of expiratory flow limitation was quantified in terms of the portion of volume over which expiratory flows with and without negative expiratory pressure were similar, and it was expressed as a percentage of the control tidal volume (VT) (expiratory flow limitation, %VT) (24). The mean values of the two negative expiratory pressure tests were used. Result reproducibility was very high because measurements were made in relaxed patients.

The total resistance of the respiratory system (Rs) was calculated by dividing the difference between Pao,max and Pao,plat by V'. Rs was partitioned into its inspiratory (Rint,rs) and additional tissue (ARrs) components (22). Rint,rs was calculated by dividing the difference between Pao,max and PI by V'. ARrs was equal to the difference between Rs and Rint,rs. The

### Measurements

Arterial blood gases were measured using a blood gas analyzer available at patient bedside (Ciba Corning 248; Bayer France). End-expiratory occlusion was performed manually using ventilator controls, thus allowing for the quantification of PEEPi and enabling the test breath to be initiated from a condition of fixed static elastic equilibrium. When PEEPi was applied, the end-expiratory occlusion pressure was determined by the sum (termed total PEEP) of the PEEPi and the ventilator-set PEEPe. It should be noted that upon ZEEPe, the ventilator generated a slightly positive end-expiratory pressure which averaged 0.50±0.3 cmH2O (thus, total PEEP was also measured on ZEEPe). Total PEEP was measured as the plateau pressure in Pao obtained 3 s after the onset of end-expiratory occlusion relative to the Pao immediately preceding occlusion. Respiratory mechanics were assessed using the end-inspiratory rapid airway occlusion technique as previously described (22). Briefly, after end-inspiratory occlusion, Pao went down from a maximal value (Pao,max) to P1, which is the value of Pao at the first zero V'. This was followed by a slow decay to an apparent plateau pressure (Pao,plat) within several seconds of occlusion. The value of Pao,plat was taken 5 s after the end-inspiratory occlusion. End-inspiratory occlusion was performed manually using the ventilator controls. Expiratory flow limitation was determined using the negative expiratory pressure test (23).

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### Inhaled fenoterol and PEEP

#### Procedure

Initially, the measurement setup was inserted and baseline measurements were performed. In both groups, end-expiratory occlusion was performed before fenoterol administration to determine the baseline total PEEP and PEEPi. In the PEEPi group, PEEPi was set according to the previously measured PEEPi and applied for 15 min. Additionally, in the PEEPi group, baseline measurements were performed after 15 min of PEEPi application.

First, arterial blood was withdrawn to determine blood gases. Second, two negative expiratory pressure tests were performed, each of them followed by four baseline breaths. A 3 s end-expiratory occlusion followed by a 5 s end-expiratory occlusion were then performed followed by 10 baseline breaths. Finally, the ΔFRC manoeuvre was performed. A nurse and physician not involved in the study were present to provide for patient care. Transcutaneous arterial oxygen saturation, systolic and diastolic arterial blood pressure and heart rate were continuously monitored.

### Table 1

<table>
<thead>
<tr>
<th>Patients</th>
<th>ETT Internal diameter (mm)</th>
<th>VT (mL)</th>
<th>RR (breaths/min)</th>
<th>T/E/Ttot</th>
<th>T I (s)</th>
<th>T E (s)</th>
<th>V (L/s)</th>
<th>F O2</th>
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<tr>
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<td>8.0</td>
<td>500</td>
<td>9.1</td>
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<td>3.50</td>
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<td>4.00</td>
<td>0.60</td>
</tr>
<tr>
<td>3</td>
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<td>6.0</td>
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<td>2.60</td>
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<tr>
<td>4</td>
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<td>595</td>
<td>7.4</td>
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<td>2.60</td>
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<tr>
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<td>700</td>
<td>8.3</td>
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<td>4.00</td>
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<tr>
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<td>1.30</td>
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<tr>
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<td>2.60</td>
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<tr>
<td>8</td>
<td>8.0</td>
<td>530</td>
<td>8.0</td>
<td>12</td>
<td>0.20</td>
<td>1.00</td>
<td>4.00</td>
<td>0.53</td>
</tr>
<tr>
<td>9</td>
<td>7.5</td>
<td>380</td>
<td>6.4</td>
<td>15</td>
<td>0.25</td>
<td>1.00</td>
<td>3.00</td>
<td>0.38</td>
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<td>10</td>
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<td>360</td>
<td>8.6</td>
<td>15</td>
<td>0.25</td>
<td>1.00</td>
<td>3.00</td>
<td>0.38</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>–</td>
<td>497±122</td>
<td>7.9±0.9</td>
<td>13±1</td>
<td>0.25±0.05</td>
<td>1.15±0.22</td>
<td>3.55±0.48</td>
<td>0.45±0.14</td>
</tr>
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</table>

FO2: Fraction of oxygen in air; RR: Respiratory rate; T/E: Expiratory duration; T I: Inspiratory duration; T/E/Ttot: Duty cycle; V': Inspiratory air flow; VT: Tidal volume
resistance of the endotracheal tube was not taken into account because each patient was his/her own control during the study. Static elastance of the respiratory system (Est,rs) was computed by dividing the difference between PaO₂,plat and total PEEP by VT. PEEPi was equal to the difference between total PEEP and PEEPe.

Statistical analysis
Values are expressed as mean ± SD. Relative variations were calculated by dividing the difference between postinhalation and preinhalation by the preinhalation value. Values were compared using Student’s paired t test and Bonferroni’s correction for multiple comparisons. Statistical analysis was performed using SPSS software (SPSS version 12.0.1, SPSS Inc, USA). P<0.05 was considered significant.

RESULTS
Respiratory mechanics
Baseline values of total PEEP on ZEEPe amounted to 8±3 cmH₂O in the ZEEPe group and 8±4 cmH₂O in the PEEPe group (P>0.05). The PEEPe level applied to the 10 patients was 6±3 cmH₂O, which represented 75±10% of the total PEEP on ZEEPe. Baseline respiratory mechanics before fenoterol administration were not different between the two groups except for PEEPi which was, as expected, lower with PEEPe than with ZEEPe (Table 2). The relative reductions of Rrs were significantly greater in the ZEEPe group than in the PEEPe group (Figure 2B) from 5 min to 240 min after fenoterol administration. Est,rs remained unchanged (Table 2).

Arterial blood gas
Arterial blood gas measurements were lacking in two patients (there was no arterial line in one and there was a technical problem with the blood gas analyzer in the other). Before fenoterol inhalation, PaO₂ was 80±14 mmHg, PaCO₂ was 53±7 mmHg and the pH was 7.40±0.08 in the ZEEPe group, PaO₂ was 79±10 mmHg, PaCO₂ was 53±97 mmHg and the pH was 7.40±0.06 in the PEEPe group (P>0.05). No significant change occurred thereafter in both groups.

Vital signs
Before fenoterol inhalation in the ZEEPe group versus the PEEPe group, respectively, the heart rate (88±15 beats/min versus 98±16 beats/min), trancutaneous arterial oxygen saturation (96±2% versus 95±2%), and systolic (123±25 mmHg versus 111±11 mmHg) and diastolic (59±13 mmHg versus 53±10 mmHg) arterial blood pressure did not significantly differ. There was no significant change in vital signs following fenoterol inhalation in either group.

DISCUSSION
Overall, the present study found that during AVF in patients with COPD, the nebulization of fenoterol resulted in greater decreases of total PEEP, PEEPi and AFRC with ZEEPe than with PEEPe. In addition, the nebulization of fenoterol suppressed tidal expiratory flow limitation in some patients when combined with PEEPe.

The small airways present in patients with COPD are flexible collapsible tubes. These airways tend to collapse at a particular...
critical closing pressure associated with a critical closing volume. The expiratory flow through collapsible tubes is described by the Starling resistor physiological model, which was recognized a long time ago (25), and is well illustrated using the waterfall analogy (15). The critical closing site of the airways causing expiratory flow limitation has been compared with the crest of a waterfall. As long as increases in pressure downstream (PEEPe) of the site of critical closure, the expiratory flow and the pressure upstream of the site of closure do not change. This theory assumes that the critical closing point is the same as PEEPi; however, the transpulmonary pressure at which expiratory flow limitation occurs must be less than the total elastic recoil pressure due to the resistive pressure losses across the upstream segment proximal to the point of dynamic collapse (14) (ie, PEEPi should be higher than the critical closing point). Moreover, there is marked heterogeneity in the presence and magnitude of expiratory flow limitation (26). Therefore, the situation is more complex than that described by the waterfall analogy. It implies that in a patient with COPD, the critical value of PEEPe, above which changes in lung volume can occur, must be less than PEEPi on ZEEPe. These above considerations have two implications. First, the absence of change in end-expiratory lung volume may not exclude regional lung hyperinflation. Second, expiratory flow limitation may be restrained once PEEPe exceeds the critical closing point, even though PEEPe is still lower than PEEPi. This latter hypothesis may explain some clinical findings previously observed. First, the application of PEEPe below PEEPi in patients with COPD during AVF can decrease the inspiratory work of breathing by reducing the inspiratory mechanical load represented by PEEPi with (27) or without (28,29) increases in end-expiratory lung volume. Second, levels of PEEPe as low as 50% of PEEPi result in the best improvement in gas exchange without hemodynamic impairment (17). Bronchodilators are of central importance in treating patients with COPD during AVF. Therefore, it was worthwhile to verify that their efficiency was not affected by the use of PEEPe. We hypothesized that the physiological efficiency of bronchodilators may be increased with PEEPe which, based on the above considerations, would promote a more distal sedimentation of $\beta_2$ agonists within the peripheral airways, where narrowing causes most of the Rrs increases in patients with COPD.

The greater reduction in lung hyperinflation obtained with fenoterol plus ZEEP rather than with fenoterol plus PEEP can be explained by the complex interplay between PEEPi and PEEPe,
with each intervention inducing opposing changes in lung volume. Hence, the present results suggest the following scenario of events. First, there is a reduction in ∆FRC, total PEEP and PEEPi with fenoterol plus ZEEPe. Second, PEEPe, which has been fixed according to total PEEP on ZEEPe before fenoterol and left unchanged after fenoterol, becomes greater than PEEPi. Third, because PEEPe is now above the critical closing volume, AFRC and, hence, total PEEP and PEEPi can increase but not decrease (14). The final result is that the reduction in lung volume elicited by fenoterol is blunted by the concomitant increase in AFRC due to PEEPe being greater than PEEPi. If this scenario is true, it has important practical implications because great care must be taken not to further increase lung volume in this setting. The first implication is that fenoterol should be delivered under a ZEEPe condition. The second implication is that, if PEEPe cannot be removed, the patient’s status must be carefully re-evaluated to detect and prevent any further lung hyperinflation. This assessment can be easily performed using the manoeuvre previously described.

The prevalence of expiratory flow in patients with COPD during AVF has been found to be consistently high (23,30-32). As previously outlined, both the response to and the selection of an appropriate level of PEEPe are centrally dependent on the presence of expiratory flow limitation. In nine patients with COPD, Georgopoulos et al (31) studied the effects of PEEPe set at 35%, 58% and 86% of PEEPi on V-volume curves. All but one patient were flow-limited during passive tidal expiration. The expiratory flow limitation progressively decreased with PEEPe in the majority of patients. As a whole, the increase in end-expiratory lung volume was small and did not worsen hemodynamics. In 10 additional patients with COPD, the same group reported that PEEPe up to 10 cmH2O (ie, 200% of PEEPi) on ZEEPe suppressed expiratory flow limitation (32). However, end-expiratory lung volume markedly and harmfully increased by an average of 0.60 L (32). PEEPe at 5 cmH2O (ie, 100% of PEEPi on ZEEPe) suppressed expiratory flow limitation in some patients and end-expiratory lung volume increased by only an average of 0.10 L (32). In our study, expiratory flow limitation was suppressed by fenoterol plus ZEEPe in only one patient. This lack of expiratory flow limitation reversal with β2 agonists has previously been described in stable patients with COPD after salbutamol treatment (33). In our study, expiratory flow limitation was suppressed with PEEPi in two patients before fenoterol nebulization. Georgopoulos et al (31) also found that in two patients, expiratory flow limitation was volume-dependent, such that expiratory flows increased at the highest level of PEEPe. Finally, in our study, three patients became not flow-limited with the combination of inhaled fenoterol and PEEPe compared with their baseline condition. Given that expiratory flow limitation has a positive correlation with dyspnea (34), resolving this phenomenon has a true clinical relevance. Therefore, expiratory flow limitation should be assessed in both conditions of ZEEPe and PEEPi. This assessment is, however, cumbersome and, to date, cannot be performed automatically from the respirator.

The reduction of Rs was rather modest in our study. This can be explained by different reasons such as the nonlinear relationship between Rs and lung volume (22), and changes in expiratory flow limitation status over time. Moreover, in our study, resistances were measured at the end of inspiration. Indeed, Kondili et al (32) found that with PEEPi levels that increased end-expiratory lung volume, expiratory Rs progressively declined. The present study and other investigations in different patients with COPD (4,16) found that ARs was the main component of baseline Rs. This finding was not observed in other studies (7,33) where the leading component of Rs was Rint,rs. This discrepancy among investigations could be due to the V’-dependence of the components of Rs; the lower the V’, the greater the contribution of ARs to Rs (22). In the present study, like in others (4,16), the V’ was in the low range. However, it should be noted that in rodents, increased tissue resistance (reflected in ARs) is the main contributor to the increase in total lung resistance observed after hyperpnea-induced bronchoconstriction (36) or metacholine challenge (37). In examining ZEEPe in the present study, the decline of Rs after fenoterol administration was essentially due to a reduction of ARs. Indeed, the values of Rint,rs did not change after fenoterol administration on ZEEPe. We had previously observed that fenoterol-ipratropium bromide delivered by nebulization is followed by a reduction in ARs with no change in Rint,rs (4). This result suggests that a more distal deposition of the drug has allowed it to act on the peripheral small airways (ie, on the main component of the increased Rs). In normal subjects (38) and patients with COPD, ARs is thought to reflect both time-constant inequality and viscoelastic behaviour of the thoracic tissues. In patients with COPD, time-constant inequality is likely to contribute to ARs more significantly than stress relaxation. Therefore, in patients with COPD, ARs is a marker of lung heterogeneity and, thus, the reduction of ARs with fenoterol administration on ZEEPe indicates a reduction in lung heterogeneity.

Fenoterol plus PEEPe did not change Rs, Rint,rs or ARs. Given that lung volume was not allowed to decrease with fenoterol plus PEEPe, the volume-dependence of inspiratory resistances can be one explanation for this result (22), namely the decrease in ARs with fenoterol alone is offset by the increase in ARs with PEEPe alone. It has actually been reported that PEEPe set at 86% of PEEPi can increase ARs (31). In our study, the fact that Est,rs did not change suggests that tidal ventilation likely operated within the linear portion of the static pressure-volume curve of the respiratory system.

The present study has some limitations. Extrapolation of the results to spontaneously breathing patients is speculative. Whether this result can be explained by a reduction in the amount of drug delivered at the end of the endotracheal tube with PEEPe is under investigation in our laboratory (39). Another study found that salbutamol delivery to a face mask during continuous positive airway pressure was reduced without affecting efficacy in nine stable asthmatic patients (40).

CONCLUSIONS

In patients with COPD who were mechanically ventilated for AVF, fenoterol combined with PEEPe had opposing effects on respiratory mechanics. It did not significantly reduce lung hyperinflation or inspiratory resistances, and it allowed expiratory flow limitation suppression in some patients. These findings result from the net effect on end-expiratory lung volume of each intervention. This implies that if fenoterol is used in combination with PEEPe, the level of the latter should be reassessed during the time course of the drug to prevent any further lung hyperinflation.

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