

Controlled expiration in mechanically-ventilated patients with chronic obstructive pulmonary disease (COPD)

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ABSTRACT: In patients with severe chronic obstructive pulmonary disease (COPD), lung emptying may be affected by flow limitation. We tested the hypothesis that the airway compression leading to flow limitation can be counteracted by controlling the expiratory flow.

The effects of an external resistor on lung emptying were studied in six patients with COPD, who were mechanically ventilated whilst sedated and paralysed. Respiratory mechanics were obtained during ventilatory support with and without the resistor. Airway compression was assessed using the interruptor method. For the study, a turbulent resistor was applied with the highest resistance level that did not increase the end-expiratory lung volume. At this resistance level, external positive end-expiratory pressure (PEEP) was generated in all patients.

As total PEEP levels remained unchanged at both settings during the controlled expiration, the levels of intrinsic PEEP were significantly decreased from 0.96 ± 0.30 to 0.53 ± 0.19 kPa (mean \pm SD). Comparison of the expiratory flow-volume curves at both settings revealed that, during the controlled expiration, the flows were significantly decreased during the first 40% of the expired volume and significantly increased during the last 60%. As the end-expiratory lung volumes remained unchanged during both settings, these increments in flow indicated a decrease in effective resistance. Airway compression was observed during unimpeded expirations in all patients using the interruptor method. During the application of the resistor, airway compression was no longer detectable.

In patients with chronic obstructive pulmonary disease receiving ventilatory support, the application of an external resistor could decrease effective expiratory resistance by counteracting airway compression, without increments in end-expiratory lung volume.

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There is ample evidence that in patients with severe chronic obstructive pulmonary disease (COPD) lung emptying is affected by flow limitation [1–5]. Although flow limitation was initially described during forced expirations, it has also been established during relaxed expirations [1–5]. The latter has been shown in mechanically-ventilated patients with COPD, in whom the respiratory muscles were paralysed [2–5].

It is assumed that by controlling the expiratory flow the airway compression leading to flow limitation can be counteracted. As early as 1972, an expiratory flow regulator was proposed in order to regulate lung emptying during mechanical ventilation in patients with COPD; the hypothesis was that reduction of early expiratory flow would improve lung emptying [6]. This concept was, however, never verified in patient studies.

In the present study, the effects of an external resistor on lung emptying were investigated in mechanically-ventilated patients with COPD whilst sedated and paralysed. Respiratory mechanics were obtained during expirations with and without the resistor. Effective airway resistance

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was estimated at both settings. Because of the nonlinear relationship between driving pressure and flow during flow limitation, resistance cannot be properly calculated. The term effective resistance was used, derived from body-plethysmography [7]. The interruptor method was applied to detect airway compression and to compute isovolume pressure-flow curves.

Patients and methods

Patients

Six patients (five males and one female), mean age 73 yrs (range 68–85 yrs), suffering from severe COPD were studied. In three patients, lung function data were available, with forced expiratory volume in one second (FEV₁) $25 \pm 5\%$ predicted and vital capacity (VC) $65 \pm 7\%$ pred (mean \pm SD). All patients were mechanically-ventilated for acute respiratory failure due to an exacerbation of COPD.

In all patients, a Siemens Servo 900c ventilator (Siemens-Elema, Solna, Sweden) in the volume-controlled mode was used. Ventilatory settings were set by the primary physician and remained unchanged during the study, except for application of the external resistance. Tidal volume equalled 0.63 ± 0.15 L (mean \pm SD) and respiratory frequency 14.7 ± 3.0 breaths \cdot min $^{-1}$. No ventilator-positive end-expiratory pressure (PEEP) was applied. During the study, the patients were sedated and paralysed. Written informed consent was obtained prior to the study from the patient's next of kin. The study was approved by the local Ethics Committee.

Respiratory measurements

Flow (V') was measured with a heated pneumotachometer (Lilly, Jaeger, Wurzburg, Germany) connected to the endotracheal tube. Volume displacement was obtained by computerized integration of the flow signal. Airway opening pressure (P_{ao}) was measured proximal to the pneumotachometer using a pressure transducer (Validyne, Validyne Co., Northridge, USA). Data were stored and analysed using a personal computer (Commodore 486 SX33, Commodore Business Machines Inc., West Chester, USA) at a sample frequency of 500 Hz. P_{ao} at end-expiration and end-inspiration were obtained by means of the end-expiratory and end-inspiratory hold buttons, respectively, of the Servo-ventilator. The end-expiratory plateau pressure was indicated as total PEEP ($PEEP_{tot}$), being the sum of intrinsic PEEP ($PEEP_i$) and external PEEP ($PEEP_e$). The P_{ao} measured just before the end-expiratory occlusion was assumed to equal $PEEP_e$. Although no ventilator-PEEP was applied during the unimpeded expirations, low levels of $PEEP_e$ were detected at airway opening in all patients. These pressures represented the pressure gradient over the ventilator circuit and the expiratory valve of the ventilator at the end of expiration. All pressure measurements were performed in duplicate.

The lung volume above the elastic equilibrium volume at end-expiration (ΔEEV) was determined by the technique of prolonged expirations [8]. ΔEEV was calculated as mean of two determinations.

From flow-volume curves, peak expiratory flow (PEF), the expiratory flow at 50% of exhaled volume ($V'_{E,50}$), and the expiratory flow at the moment the expiratory valve of the ventilator closed, *i.e.* the end-expiratory flow ($V'_{E,end}$), were determined. All flow values were calculated from five consecutive flow-volume curves.

Interruptor measurements

A pneumatic valve placed in the ventilator circuit distal to the pneumotachometer was used for repeated occlusions of the airway during expiration (Hans Rudolph 4200A, Hans Rudolph, Kansas City, USA). The pneumatic valve was computer-controlled. Opening and closing of the valve was alternated at a time cycle of 500 ms. The dynamic properties of the interruptor device and measuring equipment were studied using a constant flow generator. Using this technique, oscillations were detected of the same magnitude, frequency and pattern during opening and closing of the interruptor valve [9].

After an end-inspiratory hold procedure applied by the ventilator, the interruptor valve was closed and the patient disconnected from the ventilator tubings in order to allow a prolonged expiratory time. The interruptor procedure was then started. After opening of the valve, flow limitation was assumed to be present when the opening transient clearly exceeded the closing transient [9, 10].

In order to analyse the effect of the external resistor on respiratory mechanics, the expiratory flows at various lung volumes were related to the corresponding driving pressures. For these isovolume pressure-flow relationships, driving pressure was calculated by subtraction of the pressure just before the occlusion from the plateau pressure during the occlusion. It is assumed that this plateau pressure equals alveolar pressure at the moment of interruption [4, 9, 10]. The flow just prior to interruption was used in this analysis.

External resistor

As external resistor, a carousel with holes of different sizes was used (Vitapep, Vitapep IS, Denmark). The carousel was connected to the expiratory outlet of the ventilator.

The pressure-flow relationships obtained with a constant flow generator at the flow ranges and the holes used in the patient studies, are presented in figure 1. As high resistance level, the smallest hole was chosen that did not increase the total PEEP level. At this resistance level, positive end-expiratory airway pressures were generated without increments in EEV. For this purpose, in five patients hole A was used, and in one patient hole B was applied. In five patients a low resistance level was also applied (line C in fig. 1). As low resistance level, the smallest hole was chosen which did not increase the end-expiratory airway pressure by more than 0.1 kPa.

In order to perform repeated occlusions during expiration with the resistor, the carousel was connected to

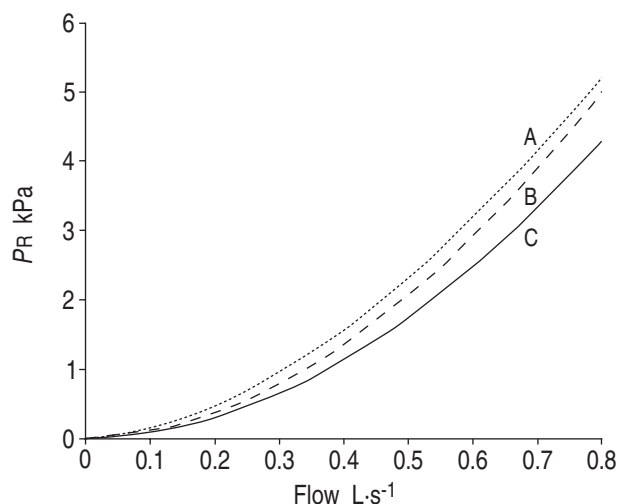


Fig. 1. — Pressure-flow relationship of the applied external resistance. (PR/V'). Pressure (PR) caused by the resistance is calculated as $PR = a \cdot V'^b$ (a and b are constants; $r > 0.97$). — — —: resistance B ($a=0.77$, $b=0.19$); ····: resistance A ($a=0.76$, $b=0.17$). The third pressure-flow relationship shown in this figure (—) belongs to hole C, which was used as the low resistance level in a group of five patients.

the outlet of the interruptor device during an end-inspiratory hold procedure. The interruptor procedure was then applied, as described previously. In this way, V' , P_{aO_2} and volume changes could be determined during application of the carousel.

Blood gas analysis

In four patients, arterial oxygen tension (P_{aO_2}) and arterial carbon dioxide tension (P_{aCO_2}) were determined during unimpeded expiration and application of the high resistance.

Protocol

At first, flow-volume curves were obtained during unimpeded expiration, after which end-inspiratory and end-expiratory holds were performed. Subsequently, ΔEEV was determined by disconnecting the patient from ventilatory tubings. After 2 min of uninterrupted ventilation, the ΔEEV determination was repeated. The interruptor procedure was then applied in duplicate, again allowing 2 min of uninterrupted ventilation in between.

After completing the measurements during unobstructed expiration, the resistor was added with the largest hole, *i.e.* the lowest resistance level. By performing end-expiratory occlusions after 1 min of controlled expiration the desired resistance level was chosen. Two minutes of controlled expiration at that resistance level were allowed before the above-mentioned procedure was repeated.

Before sampling of arterial blood, 20 min of uninterrupted ventilation was allowed. After this the ventilatory mode was changed.

Statistical analysis

Student's t-test was used, assuming significance at a p-value of less than 0.05.

Results

In all patients, PEEP_i levels were detected ranging 0.60–1.41 kPa during unimpeded expirations (table 1). During application of the low resistance, the PEEP_i levels remained unchanged. As shown in representative flow-volume curves (fig. 2), the low resistance only affected

the expiratory flow during the first 20% of expired volume. At this resistance level, the peak expiratory flow (PEF) was reduced, indicating a deceleration in time of early expiration over the first 10% of expired volume. In the next 10%, expiratory flows were found to be higher compared with unimpeded expiration. Subsequently, at 80% of expired volume the expiratory flows at low resistance were equal to those during unimpeded expiration, and the flows remained parallel during the remaining part of expiratory volume displacement. This indicated that the low resistance did not influence the effective resistance after 20% of volume was expired.

The effect of the resistance on airway compression was established with the interruptor technique. An example of the expiratory flow and pressure patterns obtained with the interruptor in patient No. 3 during an unimpeded expiration is shown in figure 3a and b. These recordings revealed supramaximal flows, immediately after opening of the interruptor valve, which largely exceeded the closing transients in all patients. Compared to unimpeded expirations, at the low resistance level the flow-overshoots remained unchanged. In figure 3c, the expiratory pressure and flow patterns of the same patient are shown during application of the high resistance level; with this resistance level no flow-overshoots could be detected.

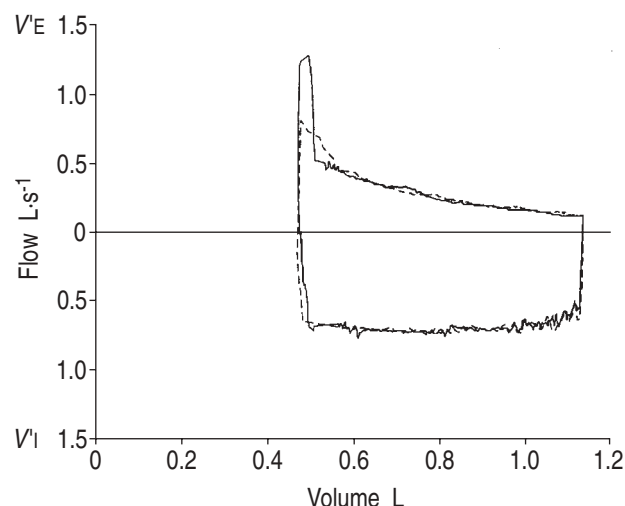


Fig. 2. — Flow-volume curves in patient No. 1. —: unimpeded expiration; - - -: low expiratory resistance. V'E: expiration; V'I: inspiration.

Table 1. — Respiratory parameters during unimpeded expiration (ue) and controlled expiration (ce) with the high resistance level

Pt No.	R level	P _{I,end} kPa		PEEP _i kPa		PEEP _e kPa		PEEP _{tot} kPa	
		ue	ce	ue	ce	ue	ce	ue	ce
1	A	1.95	2.00	1.16	0.77	0.02	0.45	1.18	1.22
2	A	2.33	2.44	1.41	0.66	0.06	0.86	1.47	1.52
3	A	1.40	1.57	0.60	0.26	0.08	0.53	0.68	0.79
4	B	1.40	1.50	0.75	0.42	0.01	0.44	0.76	0.86
5	A	1.69	1.73	0.80	0.64	0.00	0.16	0.80	0.80
6	A	1.91	1.82	1.02	0.41	0.00	0.55	1.02	0.97
Mean		1.78	1.84	0.96	0.53	0.03	0.50	0.99	1.03
SD		0.36	0.34	0.30	0.19	0.03	0.23	0.30	0.29
p-value		NS		<0.005		<0.005		NS	

Pt: patient; R: resistance; P_{I,end}: end-inspiratory pause pressure; PEEP: positive end-expiratory pressure; PEEP_i: intrinsic PEEP; PEEP_e: external PEEP; PEEP_{tot}: total PEEP; ns: nonsignificant. For explanation of resistance levels see text and figure 1.

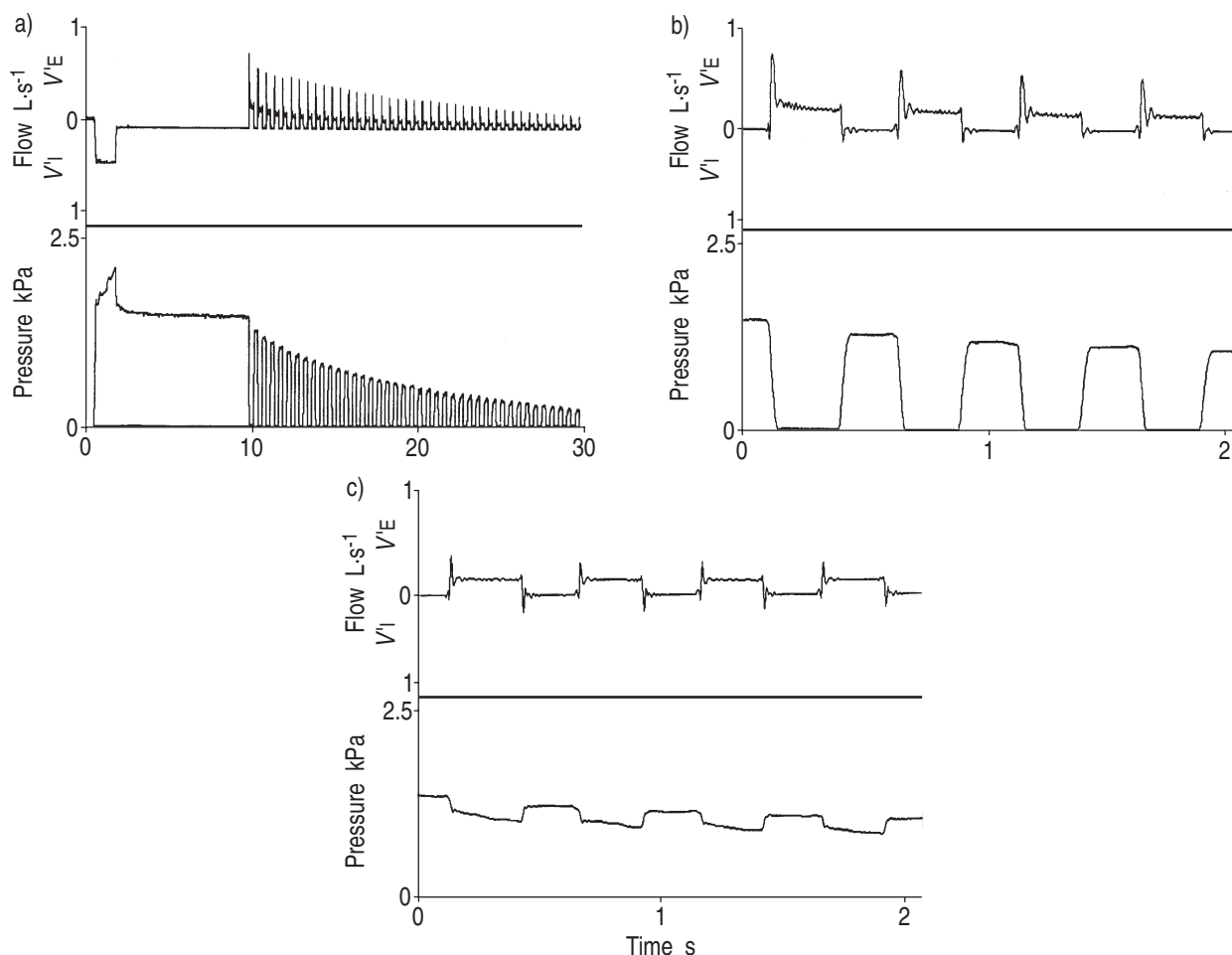


Fig. 3. – Pressure-time and flow-time diagrams during interruptor measurement in a representative patient. a) measurement during unimpeded expiration. b) Detail of the pressure-time and flow-time diagram in panel a during unimpeded expiration. c) Detail of the pressure-time and flow-time diagram in panel a during decelerated expiration. V'I: inspiratory flow; V'E: expiratory flow.

Tables 1 and 2 present data on the respiratory measurements obtained in the individual patients during unimpeded expirations, and during controlled expirations with the high resistance level. As the high resistance level did not increase PEEP_{tot} levels, the end-inspiratory pressures and the levels of Δ EEV were found to be unchanged at both settings. A decrease in PEEP_i was observed at the high resistance level as PEEP_e was generated at this setting.

Comparison of the flow-volume curves revealed substantial decreases in peak expiratory flows and small but significant increases in V'E₅₀ and V'E_{end} at the high resistance level. At this setting, expiratory flows were decreased during the first 40% of expired volume and increased during the latter 60%. As the levels of Δ EEV did not differ, the flow-volume curves at both settings could be compared isovolumetrically. Representative examples of these curves are shown in figure 4. This analysis

Table 2. – Respiratory parameters during unimpeded expiration (ue) and controlled expiration (ce) with the high resistance level

Pt No.	PEF L·s ⁻¹		V'E ₅₀ L·s ⁻¹		V'E _{end} L·s ⁻¹		Δ EEV L	
	ue	ce	ue	ce	ue	ce	ue	ce
1	1.23	0.41	0.24	0.26	0.12	0.16	0.56	0.53
2	1.40	0.73	0.26	0.29	0.17	0.23	0.99	1.04
3	0.86	0.37	0.24	0.27	0.17	0.21	0.79	0.87
4	0.78	0.31	0.19	0.20	0.14	0.16	0.80	0.87
5	0.90	0.43	0.22	0.24	0.11	0.14	0.67	0.71
6	0.96	0.38	0.24	0.26	0.16	0.19	1.28	1.21
Mean	1.02	0.44	0.23	0.25	0.14	0.18	0.85	0.87
SD	0.24	0.14	0.03	0.03	0.03	0.03	0.26	0.24
p-value	<0.0005		<0.0005		<0.005		NS	

Pt: patient; PEF: peak expiratory flow; V'E₅₀: expiratory flow at 50% of exhaled volume; V'E_{end}: end-expiratory flow; Δ EEV: dynamic hyperinflation volume (the lung volume above the elastic equilibrium volume at end-expiration); NS: nonsignificant.

indicated that the effective resistance during the latter part of expired volume with the high resistance level was reduced compared to the unimpeded expiration.

When isovolume pressure-flow relationships were computed, the low resistance level was found to decrease driving pressures, while isovolume flows remained unchanged. The high resistance level resulted in larger reductions in driving pressures with concomitant increases in isovolume flows at the lower lung volumes. Figure 5 shows the isovolume pressure-flow curves obtained in patient No. 2.

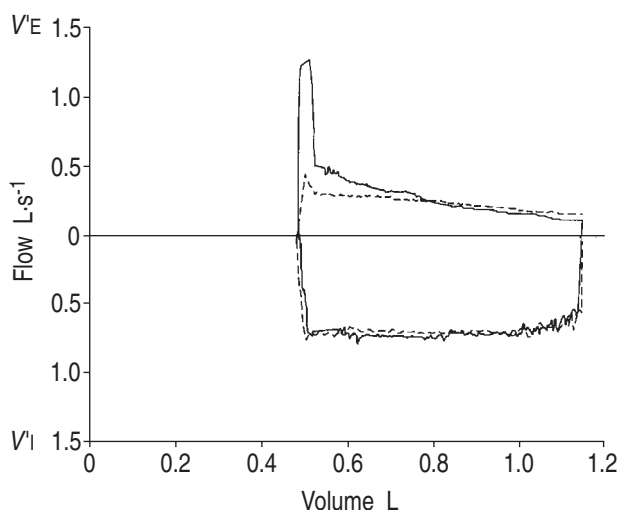


Fig. 4. — Flow-volume curves in patient No. 1. —: unimpeded expiration; - - -: high expiratory resistance. $V'E$: expiration; $V'I$: inspiration.

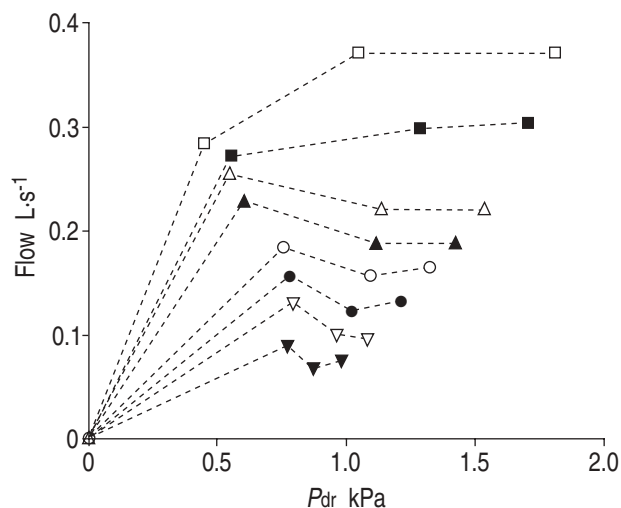


Fig. 5. — Isovolume pressure-flow diagram of patient No. 2 during unimpeded expiration and during application of high and low resistance level, at different lung volumes. Righthand symbols, *i.e.* highest driving pressures (P_{dr}) at each lung volume indicate unimpeded expiration; middle symbols at each lung volume indicate low resistance level, lefthand symbols, *i.e.* the lowest P_{dr} at each lung volume indicate application of the high resistance level. P_{dr} : driving pressure, the pressure difference between alveolar and airway opening pressure. - - □ - -: lung volume 0.55 L above end-expiratory volume (EEV); - - ■ - -: lung volume 0.45 L above EEV; - - △ - -: lung volume 0.35 L above EEV; - - ▲ - -: lung volume 0.25 L above EEV; - - ○ - -: lung volume 0.15 L above EEV; - - ● - -: lung volume 0.05 L above EEV; - - ▽ - -: lung volume 0.05 L below EEV; - - ▼ - -: lung volume 0.15 L below EEV.

No differences in blood gas tensions were established in the four patients studied. Comparison of unimpeded expiration with the high resistance level showed P_{a,O_2} to be 10.8 ± 2.6 and 10.7 ± 1.9 kPa, and P_{a,CO_2} to be 4.8 ± 0.3 and 4.8 ± 0.3 kPa, respectively (all data mean \pm SD).

Discussion

The present study demonstrates the feasibility of decreasing effective airway resistance and counteracting dynamic airway compression in patients with severe COPD by use of an expiratory resistor. These results were obtained in mechanically-ventilated patients, who were sedated and paralysed. During relaxed expirations, the presence of flow limitation, associated with airways compression, was established in all patients.

Flow limitation may occur with negative pleural pressure according to the choke-point theory [11]. In the presence of a choke-point, wave speed flow will be present. In the present study, expiratory flows are most probably not limited by the presence of wave speed but by the presence of viscous flow limitation associated with airway compression [12]. The development of flow limitation due to dynamic airway compression in this situation can be elucidated by the presence of a positive pleural pressure (P_{pl}) during lung emptying. In patients with severe COPD, a low elastic recoil pressure of the lung ($P_{L,e}$) may be found. In these patients, the elastic equilibrium volume is elevated as the low $P_{L,e}$ is associated with a normal elastic recoil pressure of the chest wall (P_{cw}) [11, 13]. In most patients with COPD, even during quiet breathing, dynamic hyperinflation is encountered, *i.e.* expiration is terminated at a lung volume above the static equilibrium volume. In that case, the P_{cw} is inward throughout the breathing cycle causing the P_{pl} to be positive during the entire expiration. Dynamic airway compression is assumed to develop when both a positive P_{pl} and a low $P_{L,e}$ are present.

Flow limitation caused by airway compression is present when isovolume pressure-flow curves reveal a plateau: above a certain critical driving pressure the flow does not increase with further increments of the pressure [2]. During forced expirations, a decrease in flow has even been observed at increasing driving pressures. This negative effort dependency has been described in patients with emphysema: during relaxed expirations the volume expired in one second can exceed that obtained during forced expirations [14].

Taking this concept into account, we investigated whether a decrease in driving pressure could preclude airway compression and, in case of negative effort dependency, could increase expiratory flow. The decrease in driving pressure was accomplished by an external resistor that reduced the pressure gradient between the alveoli and the airway opening.

In a number of studies on mechanically-ventilated patients, $PEEP_e$, *i.e.* a positive end-expiratory pressure, has been imposed in order to reduce $PEEP_i$ [2, 15, 16]. In those studies, threshold resistors have been applied to impose $PEEP_e$. A pressure level was applied at the airway opening below the level of $PEEP_i$ observed during unimpeded expirations. It was found, however, that threshold resistors did not affect either $PEEP_{tot}$ levels

or expiratory flow; the reason for this was that during the entire expiration the pressure difference between actual driving pressure and critical driving pressure was only partly counterbalanced by the PEEP_e level applied [15].

In contrast to the threshold resistors described above, the flow-dependent resistor, as used in the present study, did affect expiratory flows. This was accomplished without increments in PEEP_{tot} or in Δ EEV.

In this study, the decline in P_{ao} was controlled during expiration. This resembles pursed lips breathing, a breathing manoeuvre frequently observed in spontaneously breathing patients with COPD during dyspnoea. When patients purse their lips during expiration they experience a relief of dyspnoea [17–20]. Compared to unimpeded expiration, pursed lips breathing, was associated with a prolonged expiratory time, a decreased breathing frequency and, consequently, an increased tidal volume [17–20]. The effects of the resistor were studied in mechanically-ventilated patients with COPD, who were sedated and paralysed. Tidal volumes and expiratory times were fixed by the ventilator and did not change during application of the resistor, and respiratory mechanics could be determined when respiratory muscle activity was absent.

The effects of two resistance levels on lung emptying were analysed using volume displacements against time and expiratory flow-volume relationships. As end-expiratory lung volumes remained unchanged at the settings studied, both volume displacements and flow-volume curves could be compared at absolute lung volumes. At both resistance levels, the early PEF encountered during unimpeded expirations was abolished. This indicated a deceleration of early expiration. The low resistance level only affected lung emptying during the first 20% of expiratory volume displacement; during the latter part, the expiratory flow and effective airway resistance did not differ. In contrast to the low resistance level, the high resistance level affected lung emptying during the entire expiratory time. During the latter part of expiration, the isovolume flows were found to be increased. As the relationship between alveolar pressure and lung volume was considered to be unchanged at both settings, the increase in expiratory flows in the second part was obtained at unaltered alveolar pressures. This indicates that total effective resistance, *i.e.* the resistance over the airway and the carousel, was diminished during the controlled expiration.

Considering the latter assumption, it should be taken into account that a flow measured at airway opening, is the result of emptying of lung units with various time constants [21]. Application of the resistance could retard the emptying of fast lung units. Analysis of a simplified model consisting of two parallel resistance-capacitance (RC) units with a common serial resistance yields a delayed emptying with either equal or unequal time constants. However, at increasing serial resistance, no increase occurs in isovolume flows. Therefore, in our opinion, the increments in flow cannot be explained by the slowing of fast lung units as they were established at isovolume conditions.

As table 1 indicates, a slight increment in Δ EEV was present in 4 of the 6 patients. It may be questioned whether this increment caused the increase in flow, as was established during controlled expiration. When the

external resistance would have had no effect on flow limitation, the relationship between lung volume and flow will be comparable between unimpeded and controlled expiration. The increment in lung volume to achieve a similar increase in flow as was found experimentally, can be calculated. This calculated increment in lung volume was much higher than was established experimentally (0.15 ± 0.05 and 0.02 ± 0.06 L (mean \pm SD), respectively). Despite random inaccuracies, which may have been present in the Δ EEV determinations, in our opinion, a main effect of Δ EEV increments may therefore be excluded.

Isovolume pressure-flow curves were computed from the interruptor measurements performed during expirations with and without the resistor. In accordance with other reports, the low resistance level reduced the driving pressure without changes in isovolume flows [2, 15, 16]. The driving pressures were further reduced at the high resistance level; at lower lung volumes this was associated with increments in flow. These results are in agreement with the concept of negative effort dependency of flow at lower lung volumes.

The interruptor technique was also used to establish expiratory flow limitation by analysis of the expiratory flow pattern after a short interruption of the flow. Flow limitation is considered to be present when supramaximal flow transients are observed [9, 10]. In the present study, the flow transducer system was slightly underdamped. Because another study reported high supramaximal flows only in the case of flow limitation [9], in the present study, qualitative judgements of the presence of flow limitation from supramaximal flows were used. During unimpeded expirations, these flow-overshoots were observed in all patients studied. At the low resistance level, the flow pattern postinterruption was found to be unchanged compared to unimpeded expiration, indicating that the low resistance level did not affect flow limitation. In contrast, at the high resistance level, no flow-overshoots were observed after interruption of the flow. This observation indicates that the high resistance level did counteract airway compression.

Although determined in only four patients in the present study, deceleration of expiration did not affect arterial blood gas tensions. In accordance with observations during pursed lips breathing, it was expected that gas exchange would be enhanced due to controlled expiration. This may be explained by the fixed respiratory rate and tidal volume, and the type of resistor used. The carousel is a turbulent resistance and allowed increases in resistance by major steps. The deceleration in volume displacement may not be sufficient to improve gas exchange. A higher resistance level would have increased end-expiratory lung volume, which was considered undesirable.

The application of an external resistor was found to decrease effective airway resistance during expiration in patients with chronic obstructive pulmonary disease, who were mechanically ventilated. This decrease in effective airway resistance was associated with a reduction of airway compression, which was achieved at unaltered end-expiratory lung volumes. No effects on gas exchange were established. Further studies are required to determine whether application of a resistor can improve pulmonary gas exchange by controlling lung emptying.

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