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Effects of breathing patterns on mechanically ventilated patients with chronic obstructive pulmonary disease and dynamic hyperinflation

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Abstract *Objective:* To examine the circulatory and respiratory effects of breathing pattern in patients with chronic obstructive pulmonary disease (COPD) and dynamic hyperinflation (DH) during controlled mechanical ventilation.
Design: Prospective, controlled, randomized, non-blinded study.
Setting: Respiratory intensive care unit of a university hospital.
Patients: Nine patients with acute respiratory failure and DH due to acute exacerbations of COPD.
Interventions: Keeping tidal volume and total breath duration (T_{TOT}) constant, patients were ventilated at six different values of expiratory time (T_E). T_E changes were randomly induced by alterations of constant inspiratory flow ($\dot{V}_I$) and/or end-inspiratory pause (EIP). Patients were studied at three levels of $\dot{V}_I$(0.93 ± 0.08, 0.72 ± 0.06 and 0.55 ± 0.04 l/s, mean ± SE), with and without EIP (10% of T_{TOT}).
Measurements and results: Lung volumes, airflows, airways pressures, oxygenation indices and dead space were measured. Alveolar pressure and airway resistance (Rmin), as well as the additional resistance (δR) due to viscoelastic pressure dissipation and time-constant inequalities, were estimated by rapid airway occlusion during inflation. In seven out of nine patients, right-heart catheterization was performed and hemodynamic parameters were obtained at each value of T_E. A significant decrease of intrinsic positive end-expiratory pressure (PEEPi), end-inspiratory static and mean (mPaw) airway pressures, end-expiratory lung volume above passive FRC (Vtrap), δR and venous admixture and a significant increase of peak airway pressure, Rmin, stroke volume index and mixed venous PO_2 ($P\bar{v}O_2$) were observed when $\dot{V}_I$ increased. At each $\dot{V}_I$, the addition of EIP significantly decreased iso-volume expiratory flows and $P\bar{v}O_2$ and increased Vtrap and mPaw.
Conclusions: We conclude that in mechanically ventilated patients with COPD, the pattern of lung inflation and T_E alteration have a significant impact on respiratory system mechanics, gas exchange and hemodynamics. Addition of EIP in patients with COPD may be detrimental.

Key words Respiratory system mechanics · Gas exchange · Hemodynamics

Introduction

Dynamic hyperinflation is a common finding in patients with chronic obstructive lung disease (COPD) [1–7]. Because of severe airflow obstruction, low lung elastic recoil or high ventilatory demands, these patients do not have enough time to deplete their lungs fully to relaxed volume at the end of expiration [5]. Hence, inspiration begins at volumes at which the respiratory system exhibits a positive recoil pressure, referred to as intrinsic positive end-expiratory pressure (PEEPi) [1–7]. This phenomenon is exaggerated during mechanical ventilation by the additional resistance of endotracheal and ventilator tubes [7]. The presence of dynamic hyperinflation in mechanically ventilated patients may increase the risk of barotrauma [8] and may have detrimental effects on circulation and work of breathing [2, 3, 6, 9].

Expiratory time (T_E) is critical to the magnitude of dynamic hyperinflation [5, 9]. Increasing T_E in mechanically ventilated patients with dynamic hyperinflation should reduce PEEPi and thus decrease the risk of the above complications. Although studies indicate that ventilating these patients with long T_E using high inspiratory flows is beneficial [9, 10], the effects of such a strategy on respiratory system mechanics, gas exchange and cardiovascular status are not well established. In addition, the effect of end-inspiratory pause (EIP), which influences T_E independent of inspiratory flow rates, on the above parameters is not known. The purpose of the present study was therefore to examine the circulatory and respiratory effects of T_E changes induced by alterations of inspiratory flow or EIP in patients with COPD and dynamic hyperinflation during controlled mechanical ventilation.

Methods

Nine patients with severe COPD, requiring mechanical ventilation for management of acute respiratory failure due to acute exacerbations of chronic airflow obstruction, were studied. Their previous lung function data showed an obstructive pattern with forced expiratory volume in the first second (FEV_1) 35 ± 3%, forced vital capacity (FVC) 54 ± 5%, residual volume (RV) 185 ± 22% and total lung capacity (TLC) 115 ± 8% of predicted values (mean ± SE). The study was approved by the Hospital Ethics Committee and informed consent was obtained from the patients or their families.

The patients were studied supine during a period of clinical stability, 1–3 days after the onset of mechanical ventilation. All patients were intubated with endotracheal tubes 8–9 mm in internal diameter, sedated, paralyzed and ventilated with a constant-volume ventilator (Siemens/Servo 900C, Berlin, Germany). The ventilator was set to deliver a specific tidal volume (V_T) with a square wave flow-time profile. Minute ventilation was adjusted in each individual to maintain normal arterial pH. The patients' physical characteristics and baseline ventilator settings are shown in Table 1.

In seven out of nine patients, right-heart catheterization was performed with a 7-F triple-lumen flow-directed catheter inserted into the pulmonary artery via the internal jugular vein. In all patients ($n = 9$) a plastic catheter was inserted into a radial artery to record systemic arterial pressure and to sample arterial blood.

Flow at the airway opening was measured with a heated pneumotachograph (Fleisch no. 2, Lausanne, Switzerland) and a differential pressure transducer (Validyne 45, Northridge, Calif.), placed between the endotracheal tube and the ventilator. Airway pressures were measured from a side port between the pneumotachograph and the endotracheal tube. Exhaled volumes were measured using a 4-l water-sealed spirometer (accuracy ± 0.015 l, Godart, GB), calibrated and investigated for leaks prior to each experiment. The degree of pulmonary hyperinflation above passive functional residual capacity (FRC) was determined by measuring the total exhaled volume during a period of apnea long enough to permit the patient to reach passive FRC [2, 8, 9]. This volume represented the volume above passive FRC at the end of inspiration (V_{TOT}). The difference between V_{TOT} and V_T represented the end-expiratory lung volume above passive FRC (Vtrap).

We furthermore measured the mechanical properties of the respiratory system by the occlusion technique at end-inspiration [4, 7]. Briefly, the airways were occluded at end-inspiration and there was an immediate drop in airway pressure from a peak (Ppk) to a lower value (P_1), followed by a gradual decline to a plateau (Pp). PEEPi was measured as previously described [7], by occluding the airways

Table 1 Patient characteristics and baseline ventilator settings (*W* women; *M* men; V_T tidal volume; T_{TOT} total breath duration; $\dot{V}_E$ minute ventilation; F_IO_2 inspiratory O_2 concentration)

No.	Age (years)	Sex	PaO_2 (mmHg)	$PaCO_2$ (mmHg)	V_T (ml)	T_{TOT} (s)	$\dot{V}_E$ (l/min)	F_IO_2
1	52	M	124	60	636	3.75	10.2	0.55
2	56	M	137	58	675	3.40	11.9	0.40
3	70	W	121	52	515	3.40	9.1	0.40
4	74	W	88	46	545	3.65	9.0	0.35
5	69	W	114	55	650	3.90	10.0	0.30
6	68	M	158	53	530	3.70	8.6	0.50
7	67	M	84	42	630	3.60	10.5	0.34
8	73	W	69	59	586	3.50	10.0	0.50
9	61	M	75	61	420	4.48	5.6	0.33
Mean	66 ± 3	4W 5M	107.8 ± 10.1	54 ± 2.2	576 ± 26	3.71 ± 0.1	9.4 ± 0.5	0.41 ± 0.03

at the end of a tidal expiration and observing the airway pressure. The above variables were recorded on an 8-channel pen recorder (Hewlett-Packard 7718A, Cupertino, Calif.). Furthermore, we calculated mean airway pressure (mPaw) during the entire inflation-deflation cycle by dividing the area under the airway pressure-time tracing, as measured by planimetry, by the total cycle duration [11].

Respiratory system static inflation end-inspiratory elastance (Est, rs), corrected for gas compression and compliance of the ventilator tubing (0.7 ml/cmH_2O), was computed according to the formula [2]:

$$\text{Est,rs} = (\text{Pp-PEEPi})/(\text{Expired tidal volume-0.7} \times \text{Pp}).$$

Airway resistance (Rmin) was obtained by dividing the difference between Ppk and P_1 by the preceding constant inspiratory flow ($\dot{V}_I$) [7, 12]. By dividing the difference between Ppk and Pp by $\dot{V}_I$, total resistance of the respiratory system (Rmax) was obtained. The difference between Rmax and Rmin (δR), caused by time-constant inequalities within the lungs and chest wall and/or viscoelastic behavior (stress relaxation) [12], was also calculated. Rmin and Rmax were corrected for the resistance of the endotracheal tube [7] and for the finite occlusion time of the occlusion valve of the Siemens 900C ventilator [13].

The ratio of dead space to tidal volume (V_D/V_T) was calculated using the Enghoff modification of the Bohr equation. Mixed expired concentration of CO_2 was measured by a CO_2 analyzer (Datex, Helsinski, Finland). V_D/V_T was corrected by subtracting the volume of the apparatus (Vap = 70 ml) and the volume of gas compressed in the ventilator tubing (Vtube). Therefore, V_D/V_T was corrected (V_Dc/V_Tc) according to the formula [2, 10]:

$$V_Dc/V_Tc = (V_D - \text{Vap-Vtube})/(V_T\text{-Vtube}).$$

Cardiovascular pressures were measured at end-expiration and referenced to ambient pressure at the midaxillary level. Cardiac output (CO) was determined in triplicate by thermodilution (Computer Kontron Supermon 7210, Italy). Oxygen consumption ($\dot{V}O_2$), O_2 content of arterial (CaO_2) and mixed venous ($C\bar{v}O_2$) blood, systemic (SVRI) and pulmonary (PVRI) vascular resistances indices, oxygen transport ($\dot{D}O_2$), cardiac index (CI), stroke volume index (SVI), right (RVSWI) and left (LVSWI) ventricular stroke work indices and venous admixture ($\dot{Q}s/\dot{Q}_T$) were calculated using standard formulas [14].

When the patients were stable, $\dot{V}_I$ was changed, while V_T and total breath duration (T_{TOT}) were kept constant. $\dot{V}_I$ changes were obtained by regulation of the inspiratory time (Ti), using the appropriate button on the ventilator. Each patient was studied at three values of Ti, amounting to 20%, 25%, and 33% of T_{TOT}. At each value of Ti, measurements were performed with and without EIP (10% of T_{TOT}). Therefore, each patient was studied at six different T_E (80%, 75%, 70%, 67%, 65% and 57% of T_{TOT}). All changes were performed randomly. Before data collection, 20 min were allowed to elapse.

In order to determine the influence of breathing pattern on the rate of lung emptying, flow-volume curves during passive expiration were constructed by plotting tidal expiratory flow against the corresponding volume above passive FRC [2, 3]. At each T_E, 6–8 consecutive breaths were analyzed and then averaged to provide the mean expiratory tidal flow–volume curve. From this curve, iso-volume expiratory flows (iso-V $\dot{V}_E$) were measured at high (Vh), middle (Vm) and low (Vl) lung volumes and compared at different breathing patterns. Because in patient no. 1 tidal flow-volume curve was shifted appreciably at a T_E of 57% of T_{TOT} owing to a significant increase in Vtrap, iso-V V_E with tidal flow–volume curve at the other breathing patterns could not be identified. In this case, iso-V $\dot{V}_E$ were measured at volumes between Vtrap and passive FRC.

Data were analyzed by two-way analysis of variance, followed by Tukey's test. $P < 0.05$ was considered significant. All values were presented as mean ± SE.

Results

The effects of breathing pattern on respiratory system mechanics are shown in Fig. 1 and Table 2. A reduction in $\dot{V}_I$ or addition of EIP caused increases in Vtrap and PEEPi. Ppk decreased and Pp and mPaw increased significantly with decreasing $\dot{V}_I$. Rmax and Est, rs were not influenced significantly by the breathing pattern, while Rmin decreased and δR increased significantly with decreasing $\dot{V}_I$. At each $\dot{V}$, addition of EIP caused a significant increase in mPaw.

Iso-V $\dot{V}_E$ measured at Vh, Vm and Vl (1010 ± 110 ml, 880 ± 103 ml and 730 ± 105 ml above passive FRC) are shown in Fig. 2. At all volumes studied, addition of EIP caused a significant decrease in iso-V $\dot{V}_E$. Iso-V $\dot{V}_E$ were not affected significantly by $\dot{V}_I$.

Table 3 shows the effects of $\dot{V}_I$ and EIP on gas exchange data. Without EIP, the increase in $\dot{V}_I$ was associated with an increase in PaO_2 and PaO_2/P_AO_2. These increases did not attain significance. At each $\dot{V}_I$, the addition of EIP caused a slight but non-significant increase in PaO_2 and PaO_2/P_AO_2. Alveolar ventilation was not influenced significantly by $\dot{V}_I$. At each level of $\dot{V}_I$, EIP caused a non-significant increase of alveolar ventilation.

The effects of breathing pattern on hemodynamic data ($n = 7$) are shown in Table 4 and Fig. 3. Without EIP, SVI and $P\bar{v}O_2$ decreased and $\dot{Q}s/\dot{Q}_T$ increased significantly with decreasing $\dot{V}_I$. With EIP, the above parameters also decreased with decreasing $\dot{V}_I$, but the difference was not significant. At each $\dot{V}_I$, $P\bar{v}O_2$ decreased significantly with EIP.

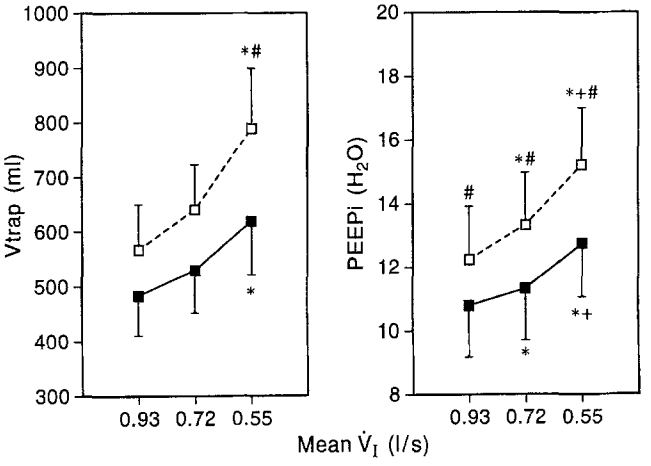

Fig. 1 Volume of gas above passive FRC at end-expiration (Vtrap) and PEEPi as a function of mean constant inspiratory flow ($\dot{V}_I$) with (*open squares connected by dashed lines*) and without EIP (*closed squares connected by solid lines*). *Bars* ± SE. * Significantly different from values at mean $\dot{V}_I$ 0.93 l/s and similar EIP conditions. + Significantly different from values at mean $\dot{V}_I$ 0.72 l/s and similar EIP conditions. # Significantly different from values without EIP at similar $\dot{V}_I$

Table 2 Effects of breathing pattern on respiratory system mechanics. Values are means ± SE ($\dot{V}_I$ constant inspiratory flow, T_E expiratory time, *Ppk*, P_I, *Pp*, dynamic and static airway pressures, *mPaw* mean airway pressure, *Rmin*, *Rmax* inflation minimum and maximum airway resistances, δR difference between Rmax and Rmin, *Est*, *rs* end-inspiratory static elastance of respiratory system).

	Without EIP			With EIP		
$\dot{V}$(l/s)	0.93 ± 0.08	0.72 ± 0.06	0.55 ± 0.04	0.93 ± 0.08	0.72 ± 0.06	0.55 ± 0.04
T_E (s)	2.97 ± 0.08	2.78 ± 0.08	2.49 ± 0.07	2.60 ± 0.07	2.41 ± 0.07	2.11 ± 0.06
Ppk (cmH_2O)	44.5 ± 3.8	40.0 ± 3.5*	35.6 ± 2.9*$^+$	44.5 ± 3.5	40.9 ± 3.8*	36.4 ± 3.1*$^+$
P_I (cmH_2O)	28.9 ± 3.1	29.5 ± 2.6	29.9 ± 2.5	29.8 ± 3.2	29.8 ± 3.1	31.1 ± 3.1
Pp (cmH_2O)	23.9 ± 2.7	24.2 ± 2.2	25.4 ± 2.4*	25.2 ± 2.7	25.6 ± 2.8	26.6 ± 2.7*
mPaw (cmH_2O)	9.6 ± 0.7	10.4 ± 0.8	11.7 ± 0.9*	12.5 ± 0.9$^\#$	13.6 ± 1.2*$^\#$	15.2 ± 1.2*$^{+\#}$
Rmax ($cmH_2O\ l^{-1}\ s^{-1}$)	20.4 ± 3.9	21.0 ± 4.4	18.7 ± 4.9	18.9 ± 3.7	19.9 ± 3.8	17.3 ± 3.9
Rmin ($cmH_2Ol^{-1}\ s^{-1}$)	14.2 ± 2.8	12.7 ± 3.0	9.0 ± 2.5*$^+$	13.3 ± 2.6	13.3 ± 2.7	8.2 ± 2.2*$^+$
δR ($cmH_2O\ l^{-1}\ s^{-1}$)	6.2 ± 1.3	8.3 ± 1.6	9.7 ± 2.5*	5.7 ± 1.3	6.5 ± 1.4	9.1 ± 2.0*
Est, rs (cmH_2O/l)	24.2 ± 2.9	23.7 ± 2.6	23.4 ± 2.8	23.9 ± 2.8	23.0 ± 3.3	21.8 ± 2.7

* Significantly different from values at $\dot{V}_I$ 0.93 l/s and similar EIP conditions
$^+$ Significantly different from values at $\dot{V}_I$ 0.72 l/s and similar EIP conditions
$^\#$ Significantly different from values without EIP at similar $\dot{V}_I$

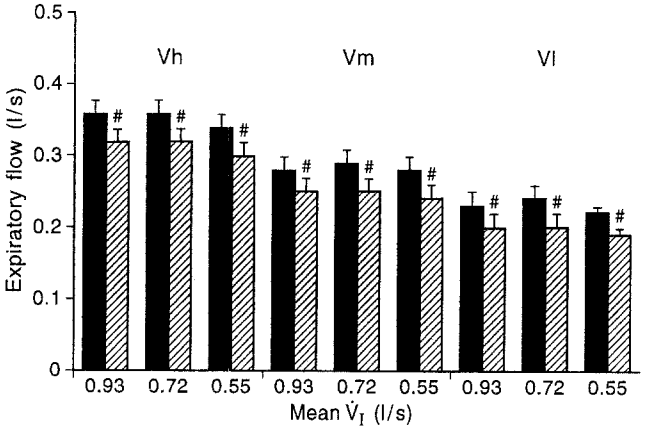

Fig. 2 Iso-volume expiratory flows (mean ± SE), measured at three lung volumes above passive FRC, as a function of mean constant inspiratory flow ($\dot{V}_I$). *Closed bars* without EIP. *Hatched bars* with EIP. *Vh*, *Vm*, *Vl*, high, middle and low lung volumes above passive FRC, respectively. See Fig. 1 for significant values

Discussion

A group of patients with severe COPD was studied. In all patients, independent of breathing pattern, the respiratory system at the end of expiration did not reach the static equilibrium volume, indicating dynamic hyperinflation. As was expected, the degree of dynamic hyperinflation was significantly affected by T_E, underlining the importance of T_E in dynamic hyperinflation in patients with COPD. However, according to the spring-and-dashpot model of the respiratory system, the pattern of lung inflation may affect expiratory flows, and thus end-expiratory lung volume, independently of T_E [15]. It has been predicted that after rapid lung inflation and in absence of EIP, the elastic recoil, and thus the driving pressure for flow, should be higher due to additional elastic energy stored at the viscoelastic elements. The present study and others [16, 17] support this prediction. Guerin et al. [16] showed in mechanically ventilated patients with COPD that application of EIP for 6 s decreased iso-volume expiratory flows. D'Angelo et al. [17] observed in normal humans that maximal expiratory flows were higher after fast-inspiration without breathholding than after slow inspiration with end-inspiratory breathholding of 4–6 s. In our study, the lowest values of iso-V $\dot{V}_E$ were observed at low $\dot{V}_I$ with EIP (Fig. 2). Nevertheless, it should be noted that we studied COPD patients in whom regional differences in time constants within the lung exist. Furthermore, at each breathing pattern,

Table 3 Effects of breathing pattern on gas exchange. Values are means ± SE ($\dot{V}$ constant inspiratory flow, T_E expiratory time, PaO_2, $PaCO_2$ partial pressures of O_2 and CO_2 in arterial blood, PaO_2/P_AO_2 pulmonary oxygenation index, V_Dc corrected dead space)

	Without EIP			With EP		
$\dot{V}_I$ (l/s)	0.93 ± 0.08	0.72 ± 0.06	0.55 ± 0.04	0.93 ± 0.08	0.72 ± 0.06	0.55 ± 0.04
T_E (s)	2.97 ± 0.08	2.78 ± 0.08	2.49 ± 0.07	2.60 ± 0.07	2.41 ± 0.07	2.11 ± 0.06
PaO_2 (mmHg)	113.1 ± 10.7	105.7 ± 11.0	98.5 ± 10.0	116.6 ± 10.3	113.8 ± 13.1	107.1 ± 9.3
PaO_2/PAO_2	0.53 ± 0.1	0.50 ± 0.1	0.47 ± 0.1	0.55 ± 0.1	0.53 ± 0.1	0.50 ± 0.1
$PaCO_2$ (mmHg)	56.2 ± 2.7	54.6 ± 1.6	54.9 ± 2.2	53.0 ± 2.2	54.0 ± 2.7	52.3 ± 2.7
V_Dc (ml)	325 ± 18	323 ± 23	334 ± 22	311 ± 20	322 ± 21	317 ± 20

Table 4 Effects of breathing pattern on hemodynamic parameters ($n = 7$). Values are means ± SE ($\dot{V}_I$ constant inspiratory flow, T_E expiratory time, *HR* heart rate, *MAP*, *CVP*, *PAP*, *Pcwp* mean systemic arterial, central venous, pulmonary artery and pulmonary capillary wedge pressures, respectively, *CI* cardiac index, SVRI, PVRI systemic and pulmonary vascular resistance indices, respectively, *LVSWI*, *RVSWI* left and right ventricular stroke work indices, respectively, $\dot{D}O_2$ O_2 transport, $\dot{V}O_2$ O_2 consumption)

	Without EIP			With EIP		
$\dot{V}_I$ (l/s)	1.01 ± 0.07	0.78 ± 0.05	0.59 ± 0.04	1.01 ± 0.07	0.78 ± 0.05	0.59 ± 0.04
T_E (s)	2.90 ± 0.05	2.72 ± 0.05	2.43 ± 0.04	2.54 ± 0.04	2.36 ± 0.04	2.07 ± 0.04
HR (b/min)	84.3 ± 2.8	90.6 ± 4.2	94.1 ± 4.1	86.0 ± 3.2	86.1 ± 3.6	89.8 ± 3.2
MAP (mmHg)	81.9 ± 4.3	87.8 ± 5.3	84.5 ± 4.0	85.1 ± 5.2	79.8 ± 2.2	83.5 ± 4.9
CVP (mmHg)	14.2 ± 1.7	13.8 ± 2.0	13.2 ± 1.3	14.3 ± 2.2	13.9 ± 1.6	15.0 ± 1.3
PAP (mmHg)	33.0 ± 4.4	32.1 ± 3.6	32.3 ± 3.3	29.3 ± 3.7	27.6 ± 3.4	30.3 ± 3.9
Pcwp (mmHg)	13.1 ± 1.7	14.1 ± 1.6	13.3 ± 1.4	14.4 ± 1.5	13.5 ± 1.3	13.7 ± 1.2
CI ($l\ min^{-1}\ m^{-2}$)	2.92 ± 0.4	2.85 ± 0.4	2.90 ± 0.5	2.85 ± 0.5	2.78 ± 0.6	2.77 ± 0.5
SVRI $dyn \times s \times cm^{-5}/m^2$	2039 ± 395	2367 ± 369	2442 ± 462	2437 ± 424	2307 ± 338	2327 ± 398
PVRI $dyn \times s \times cm^{-5}/m^2$	519 ± 82	492 ± 54	570 ± 73	451 ± 89	408 ± 62	501 ± 80
LVSWI $g \times m/m^2$	31 ± 4	31 ± 4	29 ± 4	34 ± 10	30 ± 7	28 ± 5
RVSWI $g \times m/m^2$	9.3 ± 2.6	7.9 ± 1.9	8.3 ± 2.2	7.1 ± 2.3	7.0 ± 2.7	7.2 ± 2.7
$\dot{D}O_2$ ml/min	879 ± 182	860 ± 174	844 ± 200	867 ± 219	855 ± 226	823 ± 203
$\dot{V}O_2$ ml/min	236 ± 53	203 ± 18	203 ± 20	222 ± 27	209 ± 26	233 ± 29

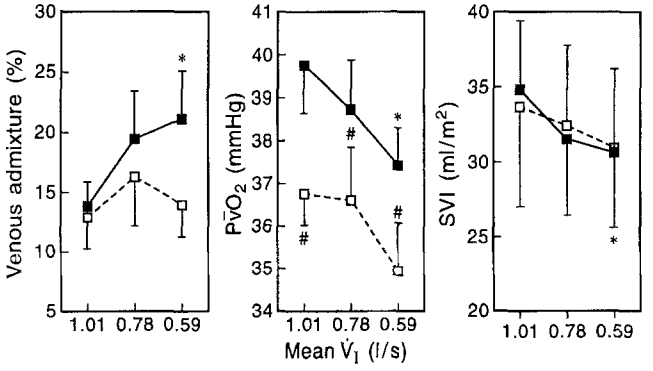

Fig. 3 Venous admixture ($\dot{Q}_S/\dot{Q}_T$), mixed venous PO_2 ($P\bar{v}O_2$) and stroke volume index (*SVI*) as a function of mean constant inspiratory flow ($\dot{V}_I$) with and without EIP ($n = 7$). See Fig. 1 for symbols and significant values

expiration started from lung volumes which differed due to differing degrees of dynamic hyperinflation. In such cases, lung emptying is determined by many factors [18]. Georgopoulos et al. [18] have recently shown in a canine model of non-homogeneous airway obstruction that during forced deflations, regional rates of lung emptying increased and decreased, respectively, in units with high and low time-constants, when the total lung volume of initiation of the maneuver was lower than that when it was higher. To the extent that mechanically ventilated patients with COPD are probably flow limited during passive expiration, and thus expiratory flows are maximal [2, 3], changes in regional rates of emptying may occur with various breathing patterns between units with different time-constants, owing to differences in volume at the beginning of expiration. These changes may affect iso-V $\dot{V}_E$ independently of the pattern of lung inflation, making the interpretation of iso-V $\dot{V}_E$ data perplexing.

According to the analysis of Bates et al. [12], the difference between Rmax and Rmin (δR) is due to stress relaxation and time-constant inequalities within the lung. In patients with COPD, time-constant inequalities should contribute significantly to this difference and thus, δR is in part an index of lung heterogeneity. In our study, as in others [2, 7, 19], δR was three to four-fold the values observed in normal humans at comparable $\dot{V}_I$ and V_T [20, 21], probably indicating a significant degree of heterogeneity in patients with COPD. Furthermore, the model of Bates et al. [12] predicts that δR increases with reducing $\dot{V}_I$, and studies in normals [20] and patients with ARDS [22] agree with that prediction. The present study suggests that patients with COPD behave similarly: δR increased in association with decreasing $\dot{V}_I$. It is not known how much lung heterogeneity contributes to this flow-dependence of δR. Gas exchange data of our study suggest that the increase in δR with decreasing $\dot{V}_I$ was due partly to worsening lung heterogeneity. At zero EIP, when $\dot{V}_I$ decreased, PaO_2 and PaO_2/P_AO_2 decreased by 13% and 12%, respectively, while venous admixture increased by 60%, in line with previous findings [9, 10]. However, the interpretation of these data should be cautious because in our study, stroke volume and $P\bar{v}O_2$ changed with $\dot{V}_I$, thereby affecting oxygenation indices independently [23].

The increase in PaO_2 and PaO_2/P_AO_2 and the decrease in venous admixture with increasing $\dot{V}_I$ occurred despite the fact that mPaw increased by 22%. In acute lung injury, mPaw is considered an important factor for gas exchange and shunt reduction, operating through alveoli recruitment [24]. Our study indicates that if lung units are already fully recruited, as in patients with COPD, increasing mean airway pressure may be detrimental.

The increase in dynamic hyperinflation and mean airway pressure caused by $\dot{V}_I$ decrease and EIP had some impact on the hemodynamic status of the patients. A small but significant decline in calculated stroke volume index was observed when T_E decreased. This was due to a concomitant slight decrease in cardiac index and increase in heart rate. Several mechanisms have been proposed to explain this reduction of stroke volume, such as decreased venous return, increased right-ventricular afterload, decreased compliance of the left ventricle and impaired myocardial contractility [25]. In our study, the maximum change of mean value of PEEPi and mPaw were approximately 5 cm H_2O. Dhainaut et al. [25] suggest that such small increases decrease stroke volume mainly through the reduction of venous return, the other mechanisms contributing when the changes in intrathoracic pressures are greater. Our results support this conclusion. We have shown that pulmonary vascular resistances remained relative stable, indicating constant right-ventricular afterload, steady position of ventricular septum, and therefore constant compliance of left ventricle [25].

Changes observed in $P\bar{v}O_2$ warrant some comment. $P\bar{v}O_2$ increased significantly with increasing T_E. $P\bar{v}O_2$ may be considered as an index of tissue oxygenation and is dependent on many factors, including the content of oxygen in arterial blood, cardiac output, oxygen consumption, and the distribution of blood flow [26]. The relation of this index to the above parameters is not always predictable [27], making the interpretation of $P\bar{v}O_2$ changes complicated. However, it is generally accepted that $P\bar{v}O_2$ above 35 mmHg indicates that sufficient O_2 is available for tissue metabolism [26]. In our study, $P\bar{v}O_2$ remained greater than 35 mmHg in all conditions studied, suggesting that significant impairment of tissue oxygenation did not occur.

It has been proposed [28, 29] that patients with increased airway resistances should be ventilated with low inspiratory flow, in order to reduce the peak airway pressure (Ppk) and thus to avoid such complications as barotrauma and hemodynamic instability. This index is misleading for two reasons. First, it is influenced by the curvilinear pressure-flow relationship of the endotracheal tube [7]. Second, we have clearly shown that Ppk does not reflect either alveolar/mean airway pressures or the degree of dynamic hyperinflation, variables that are considered critical for the above complications [8, 9, 24]. Indeed, Ppk was reduced significantly when $\dot{V}_I$ decreased, while PEEPi, mPaw, Pp and Vtrap simultaneously increased appreciably.

EIP is widely used during mechanical ventilation. It is believed that EIP, mainly through mean airway pressure increase, improves oxygenation and the efficiency of ventilation, while decreasing microatelectasis in the dependent lung regions [30]. EIP may be beneficial in patients with serious impairment of gas exchange and significantly decreased lung volumes, such as in patients with ARDS [31]. By contrast, mechanically ventilated patients with COPD are usually easily oxygenated and their lung volumes increased owing to hyperinflation [1–7]. Therefore, the addition of EIP might be detrimental in patients with airway obstruction. Indeed, we have shown that the addition of EIP increased mPaw appreciably, but this was not associated with improvement in gas exchange. On the other hand, EIP decreased T_E and iso-V $\dot{V}_E$, leading to further hyperinflation. This may increase the risk of complications associated with dynamic hyperinflation [8, 9]. However, it should be mentioned that these effects of EIP were acute and we cannot comment on the effects of EIP in the long term.

A final point is worthy of mention. We studied anesthetized and paralyzed patients, and it is not known whether these results may apply to patients capable of triggering the ventilator. It has been shown in mechanically ventilated, awake, normal humans that inspiratory flow rates exert an excitatory effect on respiratory frequency; increasing inspiratory flow is associated with an increase in breathing frequency and a decrease in expiratory time [32]. If these findings apply to patients with COPD able to trigger the ventilator, then a higher flow setting may decrease expiratory time instead of increasing it.

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