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Effects of intrinsic PEEP on pulmonary gas exchange in mechanically-ventilated patients

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ABSTRACT: The aim of the study was to assess the impact of the intrinsic positive end-expiratory pressure (PEEPi) on pulmonary gas exchange in mechanically-ventilated patients, by comparing the effects of similar levels (0.8–0.9 kPa) of positive end-expiratory pressure (PEEP) and PEEPi.

Ten patients with acute respiratory failure, without chronic airway disease, were studied with three ventilatory modes: 1) intermittent positive pressure ventilation with zero end-expiratory pressure (ZEEP mode); 2) continuous positive pressure ventilation with PEEP set by the ventilator (PEEP mode); and 3) intrinsic PEEP elicited by adequate shortening of the expiratory time (PEEPi mode). Cardiorespiratory variables (*e.g.* respiratory compliance and resistance, arterial and mixed venous blood gases, cardiac output, pulmonary capillary pressure, oxygen delivery) were measured during each ventilatory mode.

Compared to ZEEP, both PEEP and PEEPi decreased cardiac output while increasing arterial oxygen tension (Pa_{O_2}). However, the improvement of Pa_{O_2} was more consistent (8 out of 10 patients), and larger (+2.1 kPa, on average, $p<0.05$) with PEEP than with PEEPi (5 out of 10 patients, and +1.4 kPa, on average, NS).

Since the effects of PEEP and PEEPi on ventilation, lung volume, compliance, cardiac output ($\dot{Q}_T$), mixed venous oxygen tension ($P\bar{v}_{O_2}$) and oxygen consumption ($\dot{V}_{O_2}$) were similar, we attributed the less favourable impact of PEEPi on Pa_{O_2} to a less homogeneous distribution of PEEPi between lung units with different time constant, and hence to a more uneven distribution of the inspired gas.

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In mechanically-ventilated patients, the end-expiratory lung volume (EELV) can be higher than the static relaxation volume of the respiratory system (Vr), because the increase in respiratory system resistance, together with the additional resistance offered by the endotracheal tube, ventilator tubings and devices *etc.*, may prevent a complete expiration within the time available to breathe out [1, 2]. Under these circumstances, alveolar pressure is positive throughout expiration, and the intrinsic positive end-expiratory pressure (PEEPi) reflects the end-expiratory elastic recoil [2, 3]. We have shown that, during controlled mechanical ventilation, PEEPi is common not only in patients with chronic airflow obstruction (CAO), but also in patients without a history of CAO [3–6]. Since, in the latter patients, positive end-expiratory pressure (PEEP) is usually set by the ventilator to improve arterial oxygen tension (Pa_{O_2}), we wondered whether similar levels of PEEP and PEEPi might have equivalent effects on Pa_{O_2}. Although some effects of PEEPi on haemodynamics and respiratory mechanics in mechanically-ventilated patients have been reported [2, 3, 7], to our knowledge the impact of PEEPi on pulmonary gas exchange has not yet been assessed.

Therefore, we have investigated the effects of a similar level (0.8–0.9 kPa) of PEEP and PEEPi on gas exchange in mechanically-ventilated patients without CAO. The value of 0.8 kPa of end-expiratory pressure was chosen because it corresponds to the level of PEEPi previously observed in this kind of patient [4], and PEEP of this magnitude is often applied in the intensive care setting [8].

Methods

Ten mechanically-ventilated patients (table 1) with acute respiratory failure (ARF), caused by pulmonary diseases, without CAO, who were fitted with Swan-Ganz catheters upon the decision of the primary physicians, were selected for this study. Patients were studied within 48 h of

admission to the intensive care unit (ICU). The research protocol was approved by the Ethics Authorities, and informed consent was obtained from the next of kin of the patients. When admitted into the ICU, all patients exhibited diffuse bilateral infiltrates on chest X-ray, severe hypoxaemia and tachypnoea. Patients characteristics before the study are reported in table 1. All therapeutic procedures used before the present study, *i.e.* mode and setting of mechanical ventilation, sedation and paralysis, medical therapy, as well as instrumentation with a flow-directed, five-way, Swan-Ganz catheter and intra-arterial lines, were determined by the primary physicians. All patients were intubated (Portex cuffed endotracheal tube, with internal diameter ranging from 7.5–8.5 mm, Portex, Portland, OR, USA), and mechanically-ventilated according to standard criteria, 10–12 ml·kg^{-1} for tidal volume (V_T), and frequency of 12–15 breaths·min^{-1}, with a Siemens 900C Servo Ventilator (Siemens; Berlin, FRG) on control mode, with constant inspiratory flow ($\dot{V}_I$). Patients were sedated (benzodiazepine) and paralysed (pancuronium bromide) at the time of the study. The pulmonary capillary "wedge" pressure ranged from 0.9–1.9 kPa and 3.2–4.7 kPa in the patients with non-cardiogenic and cardiogenic pulmonary oedema, respectively.

increasing T_I, while $\dot{V}_E$, f, V_T, and the total cycle duration (T_{TOT}) were kept essentially constant. The T_I/T_{TOT} was increased until T_E was short enough to elicit the targeted PEEPi. In two patients the increase in T_I/T_{TOT} was not sufficient and, hence, we slightly reduced T_{TOT}. This was associated with a small decrease of V_T to minimize changes in $\dot{V}_E$. In all instances, the $\dot{V}_I$ pattern was constant and the T_I included a short (0.2–0.4 s) end-inspiratory pause. Throughout the study, fractional inspiratory oxygen (F_{IO_2}) ranged 0.5–1 between patients, but it was kept constant in each patient.

In each patient, a battery of cardiorespiratory variables was measured 20 min after the institution of each ventilatory mode. After each set of measurements had been performed, the patient was switched to the next ventilatory mode, until all three modes were completed. Respiratory mechanics were assessed as described previously [3, 4, 9]. Briefly, airway pressure and respiratory flow were measured with the transducers of the Servo 900C Ventilator [4]. Expiratory volume was obtained from electrical integration of the flow signal. The three analogic signals were recorded throughout the experiments on a four channel ink jet recorder (Mingograph Siemens).

End-expiratory and end-inspiratory airway occlusions were performed with the appropriate buttons of the

Table 1. – Patients characteristics

No.	Sex	Age yrs	F_{IO_2}	Pa_{O_2} kPa	Pa_{CO_2} kPa	pH	Diagnosis
1	M	17	1.0	6.1	5.9	7.39	Polytrauma
2	F	68	1.0	25.3	3.9	7.48	Sepsis
3	F	68	0.5	7.3	3.5	7.62	Cardiac arrest
4	F	67	0.5	7.2	3.7	7.51	CPO
5	F	51	1.0	8.3	3.7	7.58	Sepsis
6	M	62	0.5	9.8	2.7	7.58	AMI
7	F	35	1.0	14.9	4.7	7.54	Sepsis
8	M	76	0.5	8.4	11.5	7.03	Cardiac failure
9	M	68	0.6	6.7	5.3	7.27	VF
10	M	21	0.5	6.9	5.2	7.25	Polytrauma

CPO: cardiogenic pulmonary oedema; AMI: acute myocardial infarction; VF: ventricular fibrillation; Pa_{O_2}: arterial oxygen tension; F_{IO_2}: fractional inspiratory oxygen; Pa_{CO_2}: arterial carbon dioxide tension.

Once the patient was accepted into this study, the primary mode of mechanical ventilation was changed to one of the following three modes: 1) intermittent positive pressure ventilation (IPPV) with zero end-expiratory pressure (ZEEP); 2) continuous positive pressure ventilation (CPPV) with PEEP set by the ventilator at 0.8 kPa; and 3) ventilation with a short expiratory time (T_E) to elicit 0.8 kPa PEEPi. Henceforth, these ventilatory settings will be termed ZEEP mode, PEEP mode, and PEEPi mode, respectively. Minute ventilation ($\dot{V}_E$) and frequency of breathing (f) were, in general, left as set by the primary physicians. However, in the ZEEP and PEEP modes, the inspiratory and the expiratory time (T_I and T_E, respectively) were changed to obtain a T_E long enough for the end-expiratory flow to become nil, and hence to avoid PEEPi. By contrast, in the PEEPi mode, a value of 0.8 kPa of PEEPi was obtained by decreasing T_E and ventilator, and were used to measure PEEPi, static respiratory compliance (Cst,rs) and minimum (Rmin,rs) and maximum (Rmax,rs) respiratory resistances. PEEPi was measured as the plateau in airway pressure (Pplat) after 1 s from the end-expiratory occlusion. Cst,rs was computed as the ratio between the inflation volume and the difference between the end-inspiratory plateau pressure after more than 2 s of airway occlusion and end-expiratory plateau pressure [3]. Both Rmin,rs and Rmax,rs were computed by subtracting the resistance of the endotracheal tube and ventilator tubings from the total flow resistance, as described previously [4], and were corrected for valve occlusion time [10]. In normals, Rmin,rs essentially reflects airway resistance, whereas Rmax,rs represents the total respiratory resistance, which includes Rmin,rs plus the additional component due to viscoelastic behaviour of the respiratory tissue and time

constant inhomogeneity (pendelluft), *i.e.* ΔR,rs computed as the difference between Rmax,rs and Rmin,rs [9–12]. In normal subjects, ΔR,rs is almost entirely due to the viscoelastic properties of the lung and chest wall tissues, whereas, in the lung diseases, time constant inequality within the lung probably contribute significantly to ΔR,r [12].

The difference between EELV during mechanical ventilation and Vr, *i.e.* ΔEELV, was measured as described previously from the difference between EELV during tidal mechanical ventilation and the volume from a completely relaxed expiration [4]. Arterial and mixed venous blood gases were measured with an IL 1302 blood gas analyser (Instrumentation Laboratories; Lexington, MA, USA). Oxygen saturation was measured directly in both arterial and mixed venous blood *via* an OMS 2 Hemoximeter (Radiometer; Copenhagen, Denmark). Haemodynamic variables included mean pulmonary artery and capillary "wedge" pressures (Hewlett-Packard 1290A, pressure transducers, Pasadena, CA, USA). Cardiac output ($\dot{Q}_T$) was obtained in triplicate with the thermodilution technique at end-expiration (Edwards COM-1 Computer). Derived variables such as pulmonary vascular resistance (PVR), arterial and mixed venous oxygen content, pulmonary shunt fraction ($\dot{Q}s/\dot{Q}_T$), peripheral oxygen delivery ($\dot{D}o_2$), and oxygen consumption ($\dot{V}o_2$), were calculated using standard formulae [13].

Table 2. – Settings of mechanical ventilation

	ZEEP	PEEP	PEEPi
V_T *l*	0.76 (0.08)	0.75 (0.10)	0.72 (0.15)
T_I s	1.30 (0.39)	1.35 (0.29)	2.85 (0.36)*
T_E s	3.23 (0.36)	3.26 (0.31)	1.16 (0.23)*
$\dot{V}_I$ $l \cdot s^{-1}$	0.69 (0.09)	0.69 (0.10)	0.32 (0.06)*
f $b \cdot min^{-1}$	13.0 (1.5)	13.2 (1.4)	14.2 (4.8)
$\dot{V}_E$ $l \cdot min^{-1}$	9.6 (1.4)	9.6 (1.8)	10.1 (2.5)

Values are mean (SD). ZEEP: zero end-expiratory pressure; PEEP: positive end-expiratory pressure; PEEPi: intrinsic PEEP: V_T: tidal volume; T_I: inspiratory time, including 0.2–0.4 s of end-inspiratory hold; T_E: expiratory time; $\dot{V}_I$: constant inspiratory flow; *f*: frequency of breathing; $\dot{V}_E$: minute ventilation; *: $p<0.01$, significantly different from both ZEEP and PEEP.

Comparison between means was performed by paired Student's t-test when the analysis of variance (ANOVA) was significant. Differences were considered to be significant for $p<0.05$. Values are presented as means±SD, unless otherwise specified.

Results

The average values of the ventilatory patterns are shown in table 2. T_I and T_E were longer and shorter, respectively, and $\dot{V}_I$ was lower on the PEEPi mode compared to the ZEEP and PEEP modes. The T_I/T_{TOT} was approximately 0.3 on ZEEP and PEEP modes, and about 0.7 with the PEEPi mode. The small differences in $\dot{V}_E$, V_T, and *f* between the three ventilatory modes were not significant.

Measurements of respiratory mechanics are shown in table 3. Pmax increased with PEEP mode, and decreased with PEEPi mode, significantly. In contrast, Pplat increased significantly with both PEEP and PEEPi modes, compared to ZEEP. Table 3 also shows that a small PEEPi and ΔEELV (on average <0.1 kPa, and 80 ml, respectively) were present on ZEEP, although T_E was longer than 3 s. There was no PEEPi on the PEEP mode. Both PEEP and PEEPi determined an increase in EELV (*i.e.* the ΔEELV), which was slightly, though not significantly, larger on PEEPi mode than PEEP mode. Cst,rs was low in all patients and, on average, did not change significantly with different ventilatory modes. Respiratory resistances, *i.e.* both Rmax,rs and Rmin,rs were higher than normal and did not change with PEEP, in line with previous observations [4, 14]. With the PEEPi mode, compared to both PEEP and ZEEP modes, Rmax,rs increased significantly (about 0.8 $kPa \cdot l^{-1} \cdot s$, on average), mainly because of the marked increase of ΔR,rs, although Rmin,rs also increased slightly (about 0.3 $kPa \cdot l^{-1} \cdot s$, on average).

Arterial and mixed venous blood gases, and haemodynamic variables are reported in table 4. Pa_{O_2} improved with both PEEP and PEEPi modes, compared to ZEEP. However, as illustrated in figure 1, Pa_{O_2} increased in eight patients with PEEP and in only five patients with PEEPi, the improvement being significant only with PEEP

Table 3. – Respiratory mechanics

		ZEEP	PEEP	PEEPi
Pmax	kPa	3.8 (0.9)	4.3 (0.8)**	3.4 (0.6)*
Pplat	kPa	2.1 (0.6)	2.7 (0.4)**	2.5 (0.5)**
PEEP	kPa	0	0.8 (0.04)	0
PEEPi	kPa	0.07 (0.1)	0	0.9 (0.1)
ΔEELV	*l*	0.08 (0.09)	0.49 (0.24)**	0.54 (0.21)**
Cst,rs	$l \cdot kPa^{-1}$	0.41 (0.10)	0.42 (0.07)	0.42 (0.10)
Rmin,rs	$kPa \cdot l^{-1} \cdot s$	0.9 (0.4)	0.8 (0.2)	1.1 (0.4)*
Rmax,rs	$kPa \cdot l^{-1} \cdot s$	1.3 (0.6)	1.3 (0.4)	2.1 (0.6)*
ΔR,rs	$kPa \cdot l^{-1} \cdot s$	0.5 (0.3)	0.5 (0.3)	1.0 (0.3)*

Values are mean (SD). Pmax: maximum (peak) airway pressure; Pplat: plateau airway pressure after 2 s from the end-inspiratory occlusion; ΔEELV: difference between the tidal end-expiratory lung volume during mechanical ventilation and the relaxation volume on ZEEP; Cst,rs: static respiratory compliance; Rmin,rs and Rmax,rs: minimum and maximum respiratory resistance respectively; ΔR,rs: difference between Rmax,rs and Rmin,rs. For further abbreviations see legend to table 2. *: $p<0.05$, significantly different from both ZEEP and PEEP; **: $p<0.05$, significantly different from ZEEP.

Table 4. – Gas exchange and cardiovascular variables

	ZEEP	PEEP	PEEPi
Pa_{O_2} kPa	10.2 (3.7)	12.4 (4.2)**	11.6 (4.1)
Pa_{CO_2} kPa	4.2 (1.0)	4.2 (0.9)	4.0 (0.9)
$P\bar{v}_{O_2}$ kPa	4.7 (0.9)	4.6 (0.9)	4.7 (1.0)
$\dot{Q}_T$ $l \cdot min^{-1}$	6.0 (1.8)	5.6 (1.9)**	5.4 (1.6)**
$\dot{Q}s/\dot{Q}_T$ %	34 (13)	26 (11)**	30 (11)
PVR dyne·s·cm^{-5}	147 (61)	176 (52)	165 (90)
$\dot{D}_{O_2}$ ml·min^{-1}	759 (223)	752 (235)	708 (222)
$\dot{V}_{O_2}$ ml·min^{-1}	201 (60)	225 (59)	205 (79)

Values are mean (SD). Pa_{O_2}: arterial oxygen tension; Pa_{CO_2}: arterial carbon dioxide tension; $P\bar{v}_{O_2}$: mixed venous oxygen tension; $\dot{Q}_T$: cardiac output; $\dot{Q}s/\dot{Q}_T$: pulmonary shunt fraction; PVR: pulmonary vascular resistance; $\dot{D}_{O_2}$: peripheral oxygen delivery; $\dot{V}_{O_2}$: oxygen consumption. For further abbreviations see legend to table 2. **: $p<0.05$, significantly different from ZEEP.

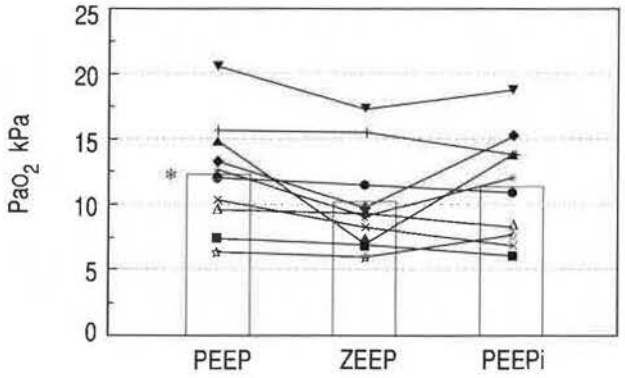

Fig. 1. – Individual values of Pa_{O_2} of 10 patients (each symbol represents a patient, top of columns is mean) while ventilated with PEEP of 0.8 kPa, ZEEP, and 0.9 kPa of PEEPi. PEEP: positive end-expiratory pressure; ZEEP: zero end-expiratory pressure; PEEPi: intrinsic PEEP; Pa_{O_2}: arterial oxygen tension. *: $p<0.05$, compared to ZEEP. For further explanations see text.

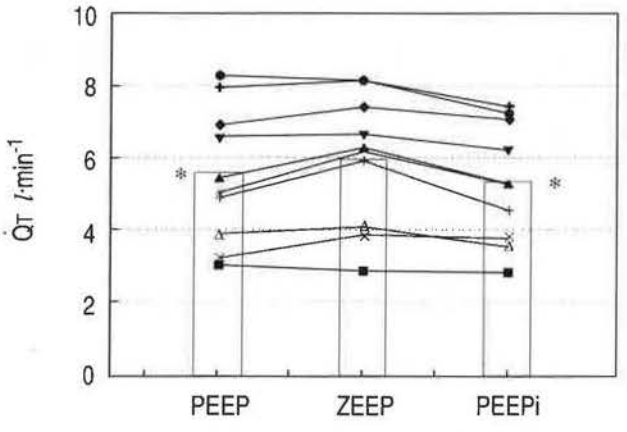

Fig. 2. – Individual values of cardiac output ($\dot{Q}_T$) of 10 patients (each symbol represents a patient, top of columns is mean) while ventilated with PEEP of 0.8 kPa, ZEEP, and 0.9 kPa of PEEPi. *: $p<0.05$, compared to zeep. For further abbreviations see legend to figure 1. For further explanations see text.

compared to ZEEP. Arterial carbon dioxide tension (Pa_{CO_2}) and mixed venous oxygen tension ($P\bar{v}_{O_2}$) did not change significantly. Cardiac output was significantly reduced by both PEEP and PEEPi (fig. 2). Also $\dot{Q}s/\dot{Q}_T$ was reduced by both PEEP and PEEPi, although, as for changes in Pa_{O_2}, the change in $\dot{Q}s/\dot{Q}_T$ was statistically significant only with PEEP compared to ZEEP. On average, changes in PVR, $\dot{D}_{O_2}$, $\dot{V}_{O_2}$, and pulmonary capillary "wedge" pressure were not significant. In this study, we did not observe any difference between patients with cardiogenic or non-cardiogenic pulmonary oedema.

Discussion

This study shows that, in mechanically-ventilated patients with acute respiratory failure, without chronic airflow obstruction, positive end-expiratory pressure of about 0.8 kPa, either set by the ventilator (PEEP) or elicited through a short T_E (PEEPi), increases Pa_{O_2} and decreases cardiac output, compared to mechanical ventilation on ZEEP. These results are in agreement with previous studies [13, 15]. However, in our study, the improvement in Pa_{O_2} was significant only with PEEP, although PEEPi was approaching the same level.

The less favourable result with PEEPi cannot be attributed to a different effect of PEEP and PEEPi on either lung volume or compliance (table 3). Indeed, the increase in EELV was similar with PEEP and PEEPi, whilst Cst,rs did not change throughout the procedure. This suggests that, for the patients in this study, the increase in lung volume was not associated with substantial changes in the pressure-volume relationship of the total respiratory system [15–17]. Changes in alveolar ventilation ($\dot{V}_A$) and pulmonary shunt, as well as in the ventilation-perfusion ($\dot{V}_A/\dot{Q}$) mismatching can also affect Pa_{O_2} [18]. As shown in tables 2 and 4, changes in $\dot{V}_E$ and in Pa_{CO_2}, and hence in $\dot{V}_A$, were small and not significant. We did not measure the distribution of the $\dot{V}_A/\dot{Q}$ ratios. The pulmonary shunt fraction ($\dot{Q}s/\dot{Q}_T$), which is also an important determinant of Pa_{O_2}, decreased with both PEEP and PEEPi, compared with ZEEP. However,

the improvement of $\dot{Q}s/\dot{Q}T$ was larger ($p<0.05$) with PEEP than with PEEPi, as was the improvement of Pa_{O_2} (table 4). The decrease of $\dot{Q}s/\dot{Q}T$ was due, at least in part, to the significant drop in $\dot{Q}T$ determined by both PEEP and PEEPi (table 4). It has been shown that a decrease in $\dot{Q}T$ can reduce $\dot{Q}s/\dot{Q}T$ through a reduction of pulmonary blood flow to unventilated alveolar units [19]. Although the fall in $\dot{Q}T$ was slightly greater with PEEPi than with PEEP, the improvement in $\dot{Q}s/\dot{Q}T$, relative to ZEEP was significant only with PEEP. Other extrapulmonary factors affecting Pa_{O_2} [18], such as $P\bar{v}_{O_2}$ and $\dot{V}_{O_2}$, did not change significantly with either PEEP or PEEPi, compared to ZEEP, probably because Pa_{O_2} and cardiac output changed in opposite directions [20].

In short, the superior impact of 0.8 kPa PEEP on arterial oxygenation, compared to a similar level of PEEPi, cannot be explained by different effects on lung volume, compliance and haemodynamics.

A possible explanation for the different effect of PEEP and PEEPi on arterial oxygenation may be provided by a different distribution of ventilation between PEEP and PEEPi modes, because of the differences in TE. The increase in EELV determined by application of PEEP is associated with an increase in the elastic equilibrium volume of the total respiratory system. In contrast, the increase in EELV elicited by PEEPi is due to the excessively short TE. Whereas PEEP is likely to be homogeneously distributed in the lung, PEEPi is probably not homogeneous, being greater in units with long time constant than in units with short time constant, because of the different rates of emptying [7].

With PEEP, the mechanical lung inflation starts from the relaxation volume of the respiratory system, and all of the ventilating units will start filling simultaneously, at a rate dependent on their regional mechanical properties [21]. In contrast, if PEEPi is present at the onset of the mechanical lung inflation, only the units with short time constant will be filling, while the long time constant units will still be emptying, until the regional PEEPi will be counterbalanced by the pressure applied by the ventilator [3, 9]. It might be predicted that a greater amount of inspired oxygenated air will reach the short time constant units rather than the units with a longer time constant, causing $\dot{V}A/\dot{Q}$ mismatching to be greater with the PEEPi mode than with the PEEP mode. The uneven distribution of ventilation might offset, in part, the benefit of the increased EELV on Pa_{O_2}. However, this is only a hypothesis, since we did not measure distribution either of ventilation or of $\dot{V}A/\dot{Q}$ ratios.

The further elucidation of the different impact between PEEP and PEEPi on pulmonary gas exchange might be important, in view of its implications for the inverse ratio mechanical ventilation (IRV), which is a particular ventilatory pattern with a long TI, followed by a short TE. IRV has been suggested as an alternative ventilatory support technique for patients with severe hypoxaemia, to improve arterial oxygenation using lower levels of Pmax and PEEP than conventional mechanical ventilation [22–26]. The lower Pmax is expected to decrease the risk of barotrauma [27]. However, Pmax includes the resistive pressure dissipated to drive flow through the endotracheal tube and the central airways, which is unlikely to produce alveolar disruption.

The technique of rapid airway occlusion during constant flow inflation allows the partitioning of Pmax into its elastic (Pplat) and resistive (Pmax-Pplat) components [21]. In our patients, Pplat measured during the end-inspiratory airway occlusion, which reflects the actual pressure distending the alveoli, was increased on PEEPi mode, and hence the risk of barotrauma was necessarily enhanced, compared to ZEEP. Therefore, the lower Pmax on PEEPi mode, which is similar to IRV, was due entirely to a decrease of the resistive pressure drop (Pmax-Pplat) caused by the lower $\dot{V}I$.

It has been suggested that during IRV lower levels of PEEP can be used than during conventional mechanical ventilation [23]. However, with IRV, the short TE is necessarily associated with incomplete expiration and, hence, PEEPi, such that during IRV it is mandatory to assess the "true" overall level of PEEP, *i.e.* PEEP plus PEEPi. Indeed, the presence of PEEPi during IRV, probably explains the drop in cardiac output observed in some patients treated with IRV [2, 26].

In summary, we have shown that, compared to ZEEP, similar levels of PEEP and PEEPi determine a similar drop in cardiac output, whereas the improvement in arterial oxygenation is more significant with PEEP, compared to ZEEP. This might be due to a different distribution of PEEP and PEEPi in the lungs, and to a more uneven distribution of ventilation in the presence of PEEPi.

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