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Effect of Inverse I:E Ratio Ventilation on Pulmonary Gas Exchange in Acute Respiratory Distress Syndrome

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Background: It is not known whether inverse I:E ratio ventilation (IRV) offers any real benefit over conventional mechanical ventilation with positive end-expiratory pressure (CMV-PEEP) at similar levels of end-expiratory pressure.

Methods: The effects of volume-controlled and pressure-controlled IRV (VC-IRV and PC-IRV, respectively) on \dot{V}_A/\dot{Q} inequality were compared with those of CMV-PEEP at a similar level of end-expiratory pressure and with CMV without PEEP (CMV) in eight patients in the early stages of acute respiratory distress syndrome (ARDS). Respiratory blood gases, inert gases, lung mechanics, and hemodynamics were measured 30 min after the onset of each ventilatory mode.

Results: Recruitment of nonventilated, poorly ventilated (or both) but well-perfused alveoli increased the partial pressure

of oxygen (P_{aO_2}) during CMV-PEEP (+13 mmHg) and IRV-VC (+10 mmHg; $P < 0.05$) compared with CMV. In contrast, PC-IRV did not affect P_{aO_2} but caused a decrease in P_{aCO_2} (-7 mmHg; $P < 0.05$). The latter was due to a concomitant decrease in dead space ($P < 0.01$) and shift to the right of \dot{V}_A/\dot{Q} distributions. During PC-IRV, the increase in the mean of blood flow distribution (mean \dot{Q} ; $P < 0.01$) without a change in the dispersion (log SD \dot{Q}) did not result in an increase in P_{aO_2} , probably because it reflected redistribution of blood flow within well-ventilated areas.

Conclusions: Short-term PC-IRV improved carbon dioxide clearance, but the lung became less efficient as an oxygen exchanger. Furthermore, based on mean airway and plateau pressures, the risk of barotrauma was not reduced with this type of ventilation. (Key words: Acute respiratory failure; arterial oxygenation; inert gases; mechanical ventilation.)

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ALTHOUGH mechanical ventilation is not a curative therapy but rather a way to provide time for the lungs to recover from acute injury, the adequate setting of the ventilator is a fundamental aspect of appropriate patient management.^{1,2} In the past 10 yr, the inverse I:E ratio mechanical ventilation (IRV) has been used increasingly as an alternative ventilatory technique in patients with acute respiratory distress syndrome (ARDS)³ to improve oxygenation at lower than conventional peak airway pressure (peak Paw).

Three potential mechanisms have been invoked to explain the increase in the partial pressure of oxygen (P_{aO_2}) with IRV³⁻⁶: (1) higher mean airway pressure (mean Paw); (2) intrinsic positive end-expiratory pressure (PEEP_i) elicited by the short expiratory time; and (3) improved intrapulmonary distribution of the inspired gas due to the lower mean inspiratory flow. However, based on the discrepant results obtained in several clinical studies,^{5,7-14} it is not yet evident whether IRV offers any real, even short-term, benefit over conventional controlled mechanical ventilation (CMV) with PEEP. This is particularly true when comparison is made at similar

levels of end-expiratory pressure^{6,13} and volume.^{11,14} Given these discrepant results and because improvement of oxygenation is the major aim of IRV, a better understanding of the mechanisms underlying the effects of IRV on pulmonary gas exchange is warranted. Accordingly, we investigated the effect on gas exchange of four ventilator settings: (1) volume-controlled mechanical ventilation without PEEP (CMV); (2) volume-controlled mechanical ventilation with PEEP (CMV-PEEP); (3) volume-controlled inverse I:E ratio ventilation (VC-IRV); and (4) pressure-controlled inverse I:E ratio ventilation (PC-IRV). The comparison was made at the same level of total PEEP while keeping tidal volume, respiratory rate, and inspiratory oxygen fraction (FiO₂) unchanged.

Materials and Methods

Population

The study was approved by the Ethics Committee of the Hospital Clinic, and written informed consent was obtained from each patient's next of kin. Eight mechanically ventilated patients were studied early in the course of ARDS; that is, within 48 h from onset of acute respiratory failure. The inclusion criteria, which were in keeping with the International Consensus Conference,² included presence of severe hypoxemia (PaO₂/FiO₂ ratio < 200 mmHg) and bilateral pulmonary infiltrates. None of the patients had preexisting chronic respiratory disease, left-ventricular failure defined by a pulmonary artery occlusion pressure (PAOP) > 15 mmHg, or the presence of thoracic drains or rib cage instability. Severity of ARDS expressed as lung injury score¹⁵ was 2.6 ± 0.4 (SD). All patients were orotracheally intubated with a Portex cuffed endotracheal tube and were mechanically ventilated with a Siemens 900C Servo Ventilator (Siemens-Elma BA, Solna, Sweden) using the volume-controlled mode with constant inspiratory flow (\dot{V}_I) and PEEP before the study. Table 1 shows patients characteristics.

Hemodynamics

The electric activity of the heart was monitored continuously. An 18-gauge plastic cannula was inserted into the radial artery for monitoring systemic blood pressure and for arterial blood sampling. A 7-French triple-lumen thermodilution, balloon-tipped pulmonary artery catheter (Edwards; Baxter Healthcare, Irvine, CA) was inserted percutaneously and progressed into the pulmo-

nary artery to measure pulmonary artery pressure, pulmonary artery occlusion, and right atrial pressure (model 56S; Hewlett-Packard, Andover, MA). Average measurements of three consecutive breaths were taken at end expiration. Thermodilution cardiac output (\dot{Q}_T) was measured by injecting 10 ml cold 0.9% saline solution into the proximal end of the pulmonary artery catheter. Reported \dot{Q}_T values are the means of four consecutive measurements. Pulmonary vascular resistance was calculated according to the standard formula.

Respiratory Mechanics

Airway pressure was measured with a differential pressure transducer (model 143PCO3D; Honeywell, Freeport, IL) through a side port at the proximal end of the endotracheal tube. Flow (\dot{V}) was measured with a Fleisch no. 1 heated pneumotachograph (Metabo, Lausanne, Switzerland) connected to a differential pressure transducer (model 304A; Hewlett-Packard, Palo Alto, CA) and inserted between the endotracheal tube and the Y connection of the ventilator. Tidal volume was calculated by mathematical integration of the flow signal. Inspiratory time (T_I), expiratory time (T_E), total breathing cycle duration (T_{TOT}), respiratory frequency (f), and minute ventilation (\dot{V}_E) were also calculated. Peak Paw and plateau pressure (P_{plat}) during brief end-expiratory and end-inspiratory airway occlusion were recorded.^{16,18} At the end of a tidal expiration, the expiratory line of the ventilator was occluded using the end-expiratory hold button of the ventilator for direct measurement of PEEP_i as the difference between the plateau in mean Paw during the occlusion (approximately 1 s) and the mean Paw level before interruption. Without PEEP set by the ventilator, the plateau in mean Paw during the occlusion, compared with atmospheric pressure, reflects PEEP_i (i.e., the end-expiratory elastic recoil pressure). When PEEP has been set by the ventilator, the plateau in mean Paw during the end-expiratory occlusion represents the total PEEP (PEEP_T), whereas the difference between the plateau and the preinterruption level provides PEEP_i, according to the formula (PEEP_T = PEEP + PEEP_i). After the end-expiratory plateau was observed, the occlusion was released for mechanical lung inflation. Then the end-inspiratory occlusion was performed using the end-inspiratory hold button of the ventilator. Immediately after, a rapid decrease in mean Paw was observed, followed by a gradual decrease to a plateau (P_{plat}), reflecting the end-inspiratory elastic recoil at the end-inflation lung volume. As soon as such a plateau was achieved (approximately 2-

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Table 1. Clinical Data of Patients

Patient No.	Age (yr)	Sex	Diagnosis	PaO ₂ /F _{IO} ₂	PEEP (cmH ₂ O)	LIS	ETT (mm)	Outcome
1	24	M	Thoracic trauma	169	6	2.5	8.5	S
2	74	M	Aortic aneurysm	125	8	2.8	8.0	D
3	62	M	Coronary bypass	57	10	3.0	8.5	D
4	85	F	Aortic aneurysm	128	4	2.0	8.0	D
5	58	M	Brain hemorrhage	77	10	3.0	8.0	D
6	62	M	Septic shock	161	6	2.5	8.5	S
7	74	M	Aortic aneurysm	117	8	2.0	8.0	D
8	47	M	Esophageal cancer	195	10	2.8	8.5	D
Mean ± SD	61 ± 19			129 ± 46	7.8 ± 2.3	2.6 ± 0.4		

LIS = Lung Injury Score; ETT = diameter of the endotracheal tube, D = died; S = survived.

3 s), the occlusion was released. These maneuvers (end-expiratory and end-inspiratory airway occlusion) were repeated three to five times, leaving seven regular mechanical ventilatory cycles in between.

Respiratory Gases

Inspired oxygen fraction (F_{IO}₂) and mixed expired oxygen (F_{EO}₂) and carbon dioxide (F_{ICO}₂) fractions were measured using mass spectrometry (Multigas Monitor MS-2; BOC-Medishield, London, UK). A small arterial catheter, indwelling in the radial artery for clinical purposes under local anesthesia, was used to sample arterial blood with a heparin-prepared syringe to measure arterial oxygen pressure (P_O₂), carbon dioxide pressure (P_{CO}₂), and pH by standard electrode technique (IL-306, Instrumentation Laboratories, Milano, Italy). Mixed venous blood was sampled from the distal lumen of the Swan-Ganz catheter to measure mixed venous P_O₂. Venous admixture (\dot{Q}/\dot{Q}_T), oxygen delivery ($\dot{D}O_2$), and oxygen consumption ($\dot{V}O_2$) were calculated according to standard formulas.

Distribution of Ventilation-Perfusion Ratios

The multiple inert gas elimination technique is based on the simultaneous elimination of trace concentrations of six inert gases (sulfur hexafluoride, ethane, cyclopropane, enflurane, ether, and acetone) infused, in a saline solution, into a peripheral vein of the forearm.¹⁷ General features of the setup of the multiple inert gas elimination technique in our laboratory have been reported elsewhere.^{17,18} Briefly, after approximately 45 min of

infusion of the solution of the six inert gases at a rate of 3 ml/min, arterial, mixed venous (8 ml each), and mixed expired samples were simultaneously obtained in duplicate. Mixed expired gases were collected through a 1-l inner volume metallic heated box inserted in the expiratory line of the ventilator.* Duplicate samples of arterial, mixed venous blood, and mixed expired gases were processed separately. Results are reported as mean values of duplicate measurements. Shunt was defined as the fraction of blood flow to unventilated alveoli ($\% \dot{Q}_T$ to \dot{V}_A/\dot{Q} ratio < 0.005). Low \dot{V}_A/\dot{Q} and high \dot{V}_A/\dot{Q} were defined as the percentage of perfusion to poorly ventilated units ($\% \dot{Q}_T$ to \dot{V}_A/\dot{Q} ratio between 0.005 and 0.1) and the percentage of alveolar ventilation to poorly perfused units ($\% \dot{V}_A$ to \dot{V}_A/\dot{Q} ratio between 10 and 100), respectively. Dead space was defined as the percentage of alveolar ventilation to unperfused units ($\% \dot{V}_A$ to \dot{V}_A/\dot{Q} ratio > 100). The position (first moment) of the perfusion (mean \bar{Q}) and ventilation (mean \bar{V}) was defined as the mean \dot{V}_A/\dot{Q} ratio of each distribution, and their dispersion (second moment) as the standard deviation of perfusion (log SD Q) and ventilation (log SD V) distributions on a logarithmic scale. The residual sum of squares is a quantitative estimation of the overall experimental error in the assessment of \dot{V}_A/\dot{Q} distributions.¹⁷

Study Design

Patients were studied in the semirecumbent position in a stable clinical condition. They were sedated during the study with continuous intravenous infusion of midazolam (Dormicum; Roche SA, Madrid, Spain). Patients were paralyzed with pancuronium bromide (Pavulon; Organón-Hermes SA, Sant Boi de Llobregat, Spain) to avoid muscular activity during the measurements. The

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patients were studied under four different ventilatory modalities. The \dot{V}_E , V_T , f , and FiO_2 , which had been prescribed by the attending physicians, were kept unaltered throughout the procedure. In addition, the standard medical treatment (antibiotics, vasoactive drugs, diuretics, and so on) was not changed throughout the procedure, except for additional sedation and paralysis when needed. The following changes were made in the ventilator settings to implement the targeted ventilator modalities: (1) PEEP, which was always present before the study (table 1), was removed to implement the controlled mechanical ventilation mode (CMV) without PEEP; (2) the level of PEEP was set at 8 cmH₂O in all patients to obtain the CMV-PEEP mode; (3) without any PEEP set by the ventilator, the T_i was increased progressively while leaving T_{TOT} unaltered but shortening T_E until a level of PEEP_i of about 8 cmH₂O was achieved during volume-cycled ventilation with constant flow (this mode was called VC-IRV); and (4) with a setting similar to VC-IRV, the inspiratory support mode was changed to pressure control (PC-IRV) with which a PEEP_i of about 8 cmH₂O was generated. No end-inspiratory pause was used. After establishing the ventilatory parameters needed to fulfill all required protocols, the order of the modalities was randomly assigned to each patient. The arterial oxygen saturation was monitored during the study by pulse oximetry (model M1092-A; Hewlett Packard, Savonmo, Italy) and maintained above 96%. Patients were studied under steady-state conditions, which in all instances had been established after 30 min of ventilation with each ventilatory mode, as judged by the monitoring of ventilatory and hemodynamic variables, as well as mixed expiratory respiratory gases. After 30 min at each ventilating mode, measurements were made in the following order of (1) multiple inert gas elimination technique and expired, arterial, and mixed venous blood gases; (2) pulmonary and systemic hemodynamics; and (3) respiratory mechanics.

Statistical Analysis

Results are presented as means \pm SD, unless otherwise stated. A two-way analysis of variance for repeated measurements and Fisher contrast analyses were used for comparison among ventilatory modes. Student's paired t test was used when required to compare between two groups of data. Probability values < 0.05 were accepted as significant.

Results

Ventilatory Pattern and Respiratory Mechanics

By design (table 2), minute ventilation, tidal volume, and ventilator frequency were kept constant throughout the study. Accordingly, T_i and T_E were significantly longer and shorter, respectively, during IRV. A small PEEP_i was found during CMV without PEEP set by the ventilator, as previously reported in patients with ARDS.¹⁶ Peak Paw was lower during IRV than CMV-PEEP, whereas P_{plat} was not different among the three modalities (CMV-PEEP, VC-IRV, and PC-IRV). Mean mean Paw was higher during IRV than CMV-PEEP, with the highest value occurring during PC-IRV. Static elastance decreased during PEEP and IRV.

Blood Gases and Hemodynamics

Table 3 shows the blood gas and hemodynamic measurements. Arterial P_{O_2} improved with PEEP (+13 mmHg, on average) and with VC-IRV (+10 mmHg, on average). In contrast, with PC-IRV, P_{aO_2} did not change compared with CMV. Arterial P_{aCO_2} and pH were lower and higher, respectively, with IRV (particularly with PC-IRV) than with CMV. Systemic hemodynamics and oxygen delivery were not influenced by the different ventilatory modalities. Only pulmonary capillary occlusion pressure increased with PEEP and IRV.

Inert Gas Exchange

Table 4 shows the inert gas data under the four different ventilatory conditions. As expected, perfusion to unventilated \dot{V}_A/\dot{Q} units (shunt) decreased significantly with CMV-PEEP, which essentially explains the observed increase in P_{aO_2} with CMV-PEEP compared with CMV. A representative pattern of the \dot{V}_A/\dot{Q} inequality with the four ventilator settings used in this study is shown in figure 1. During CMV, \dot{V}_A/\dot{Q} distributions showed the well-known \dot{V}_A/\dot{Q} pattern previously reported in ARDS¹⁹: unimodal ventilation and perfusion distributions associated with a large intrapulmonary shunt and a small increase in dead space.

During VC-IRV, inert gas shunt and \dot{V}_A/\dot{Q} distributions did not show significant changes compared with CMV-PEEP. During PC-IRV, however, the percentage of shunt was higher than during CMV-PEEP. Compared with CMV-PEEP and VC-IRV, the inert gas results during PC-IRV suggest a redistribution of blood flow to lung units with a \dot{V}_A/\dot{Q} ratio higher than 1. Mean \bar{Q} increased in

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Table 2. Ventilatory Pattern and Respiratory Mechanics

	CMV	PEEP-CMV	VC-IRV	PC-IRV	ANOVA
\dot{V}_E (L · min ⁻¹)	10.3 (2.3)	11.3 (2.7)	11.0 (2.6)	11.2 (2.9)	NS
f (min ⁻¹)	15.7 (2.5)	16.2 (2.6)	16.1 (1.8)	16.1 (2.0)	NS
V_T (L)	0.67 (0.20)	0.70 (0.20)	0.69 (0.20)	0.69 (0.20)	NS
T_I (s)	0.99 (0.33)	0.83 (0.08)	2.72 (0.31)*†	2.79 (0.34)*†	<0.001
T_E (s)	2.92 (0.43)	2.77 (0.57)	1.06 (0.26)*†	0.97 (0.23)*†	<0.001
T_I/T_{TOT}	0.25 (0.04)	0.24 (0.04)	0.72 (0.50)*†	0.74 (0.50)*†	<0.001
peak Paw (cmH ₂ O)	26.8 (4.9)	31.1 (3.9)*	25.2 (2.5)†	25.2 (2.9)†	<0.001
P_{plat} (cmH ₂ O)	16.4 (3.1)	20.5 (2.9)*	20.6 (2.2)*	21.5 (2.3)*	<0.001
PEEPi (cmH ₂ O)	0.61 (0.9)	0.24 (0.3)	7.6 (1.1)*†	8.0 (1.2)*†	<0.001
PEEPt (cmH ₂ O)	0.61 (0.9)	8.1 (1.2)*	7.6 (1.1)*	8.0 (1.2)*	<0.001
mean Paw (cmH ₂ O)	7.5 (3.2)	11.4 (1.9)*	15.2 (1.2)*†	19.6 (1.9)*†‡	<0.001
Est, rs (cmH ₂ O · L ⁻¹)	25.1 (9.2)	20.3 (5.8)*	20.6 (5.9)*	21.8 (7.8)*	<0.025

Values are mean (SD). ANOVA: $P < 0.05$.

\dot{V}_E = minute ventilation; f = breathing frequency; V_T = tidal volume; T_I = inspiratory time; T_E = expiratory time; T_I/T_{TOT} = duty cycle; PEEP = positive end-expiratory pressure set by the ventilator; PEEPi = intrinsic PEEP; PEEPt = (PEEP + PEEPi); peak Paw = peak cycling pressure; P_{plat} = pressure (plateau) measured 5 s after the end-inspiratory airway occlusion; mean Paw = mean airway pressure; Est, rs = static elastance of total respiratory system; NS = not significant.

* Significant at 95% for CMV versus PEEP-CMV, VC-IRV, and PC-IRV (Fisher PLSD).

† Significant at 95% for PEEP-CMV versus VC-IRV and PC-IRV (Fisher PLSD).

‡ Significant at 95% for VC-IRV versus PC-IRV (Fisher PLSD).

both CMV-PEEP and VC-IRV. Further, mean \bar{V} was higher in PC-IRV than in VC-IRV. As indicated in table 4, the dead space decreased during PC-IRV.

The arterial P_{O_2} predicted from the inert gas data was similar to the P_{aO_2} measured from arterial blood (the difference between predicted and measured P_{aO_2} was

2.7 ± 13.1 mmHg; $P = 0.3$). Quality control of inert gas measurements as assessed by the residual sum of squares showed acceptable results. Mean \pm SD value for residual sum of squares was 2.8 ± 1.7 (the upper limit for residual sum of squares is generally set at 10). Agreement between the cardiac output calculated from

Table 3. Pulmonary and Systemic Hemodynamics and Respiratory Blood Gas Data

	CMV	PEEP-CMV	VC-IRV	PC-IRV	ANOVA
FI_{O_2}	0.68 (0.17)	0.68 (0.17)	0.68 (0.17)	0.68 (0.17)	NS
Pa_{O_2} (mmHg)	85 (31.4)	98 (27.4)*	95 (36.6)*	82 (28.2)†‡	<0.05
Pa_{CO_2} (mmHg)	42 (5.1)	39 (7.9)	38 (7.1)*	35 (4.9)*	<0.05
pH	7.40 (0.09)	7.41 (0.09)	7.43 (0.09)*	7.45 (0.08)*†‡	<0.01
$P\bar{V}_{O_2}$ (mmHg)	41 (7.3)	40 (6.9)	40 (5.9)	39 (6.6)	NS
MSP (mmHg)	74 (8.2)	73.4 (4.3)	74.6 (8.8)	76.1 (8.2)	NS
\dot{Q}_T (L · min ⁻¹)	8.3 (3.5)	8.0 (3.2)	7.9 (3.5)	7.8 (3.7)	NS
PAP (mmHg)	25 (5.2)	26 (4.6)	26 (3.9)	26 (2.6)	NS
PAOP (mmHg)	11 (5.1)	14 (4.3)*	15 (4.3)*	14 (4.4)*	<0.05
PVR (dyne · s · cm ⁻⁵)	157 (74)	141 (81)	140 (65)	155 (64)	NS
\dot{D}_{O_2} (L · min ⁻¹)	1.08 (0.44)	1.07 (0.44)	1.03 (0.45)	1.01 (0.46)	NS
\dot{V}_{O_2} (L · min ⁻¹)	0.253 (0.06)	0.266 (0.07)	0.258 (0.07)	0.27 (0.07)	NS

Values are mean (SD). ANOVA: $P < 0.05$.

FI_{O_2} = oxygen inspiratory fraction; Pa_{O_2} = arterial P_{O_2} ; Pa_{CO_2} = arterial P_{CO_2} ; $P\bar{V}_{O_2}$ = mixed venous P_{O_2} ; MSP = mean systemic arterial pressure; \dot{Q}_T = cardiac output; PAP, PAOP = mean pulmonary artery and pulmonary artery occlusion pressures; PVR = pulmonary vascular resistance; \dot{D}_{O_2} = systemic oxygen delivery; \dot{V}_{O_2} = oxygen uptake; NS = not significant.

* Significant at 95% CMV versus PEEP-CMV, VC-IRV, and PC-IRV (Fisher PLSD).

† Significant at 95% PEEP-CMV versus VC-IRV and PC-IRV (Fisher PLSD).

‡ Significant at 95% VC-IRV versus PC-IRV (Fisher PLSD).

Table 4. Inert Gas Exchange Data

	CMV	PEEP-CMV	VC-IRV	PC-IRV	ANOVA
Shunt (% \dot{Q}_T)	37 (11.9)	30 (8.0)*	34 (7.2)	36 (8.1)†	<0.05
% \dot{Q}_T to low \dot{V}_A/\dot{Q}	4.0 (6.6)	5.0 (8.2)	2.3 (4.7)	3.2 (5.3)	NS
\bar{Q}	0.91 (0.40)	0.97 (0.53)	1.09 (0.55)	1.40 (0.88)*†‡	<0.01
logSD (Q)	1.08 (0.50)	1.13 (0.57)	0.95 (0.45)	1.09 (0.53)	NS
Dead space (%)	40 (11.7)	38 (9.5)	37 (6.4)	25 (9.5)*†‡	<0.01
% \dot{V}_E to high \dot{V}_A/\dot{Q}	4 (6.9)	3 (7.3)	1 (1.0)	6 (7.3)‡	NS
\bar{V}	2.33 (1.35)	2.28 (1.27)	1.99 (0.82)	2.88 (1.31)‡	<0.05
logSD (V)	0.83 (0.26)	0.77 (0.17)	0.69 (0.19)	0.76 (0.22)	NS

Values are mean (SD). ANOVA: $P < 0.05$.

Shunt = percentage of blood flow to unventilated units and areas with \dot{V}_A/\dot{Q} ratios <0.005 ; % \dot{Q}_T to low \dot{V}_A/\dot{Q} = percentage of blood flow to units with $\dot{V}_A/\dot{Q} <0.1$ (excluding shunt); \bar{Q} = mean \dot{V}_A/\dot{Q} ratio of the blood flow distribution; logSD (Q) = dispersion of the blood flow distribution; Dead space = percentage of \dot{V}_E to \dot{V}_A/\dot{Q} ratios >100 ; % \dot{V}_E to high \dot{V}_A/\dot{Q} = percentage of minute ventilation to \dot{V}_A/\dot{Q} ratios between 10 and 100; \bar{V} = mean \dot{V}_A/\dot{Q} ratio of the ventilation distribution; logSD (V) = dispersion of the ventilation distribution; NS = not significant.

* Significant at 95% CMV versus PEEP-CMV, VC-IRV, and PC-IRV (Fisher PLSD).

† Significant at 95% PEEP-CMV versus VC-IRV and PC-IRV (Fisher PLSD).

‡ Significant at 95% VC-IRV versus PC-IRV (Fisher PLSD).

the inert gas data (7.8 ± 3.6 l/min) and that obtained by thermodilution (8.0 ± 3.2 l/min; $r = 0.96$) provided further support for the accuracy of the inert gas measurements.

Discussion

We found that IRV in VC-IRV and PC-IRV modalities does not provide any short-term improvement of gas exchange relative to CMV with PEEP, when the comparison is made at similar levels of total end-expiratory pressure while tidal volume, respiratory rate, and FiO_2 were kept constant. Application of PEEP of 8 cmH₂O (CMV-PEEP) significantly increased PaO_2 (about 13 mmHg) compared with CMV alone, mainly because of a significant decrease (7%) in intrapulmonary shunt. Because cardiac output did not change significantly (table 3), the decrease in shunt should be attributed to recruitment of previously nonventilated units,¹⁹ as suggested by static elastance.

During PC-IRV, the increase in mean \bar{Q} (table 4) reflects redistribution of blood flow within regions of normal \dot{V}_A/\dot{Q} ratio, which may not improve the oxygen exchange capability of the lungs with large shunt. Further, the percentage of shunt during PC-IRV was similar to that in CMV, which explains why PaO_2 was less with PC-IRV than with VC-IRV and CMV-PEEP. The significant decrease in PaCO_2 during PC-IRV in our study was due to (1) the shift to the right of \dot{V}_A/\dot{Q} distributions and

(2) a significant decrease in the inert gas dead space with the prolonged inspiratory duration. This is corresponds with the results of previous studies^{11,13} in which a decrease in physiologic dead space with PC-IRV was also found. Overall, the gas exchange results in the present study suggest that during PC-IRV, the lungs, although not more efficient as an oxygen exchanger, become more efficient in clearing carbon dioxide. Whether the decrease in PaCO_2 with PC-IRV is clinically relevant remains to be established.

Our results are in keeping with those of previous studies^{13,14} that have shown that PC-IRV did not improve PaO_2 compared with traditional CMV with PEEP, when the comparison is made at equal levels of PEEP, while keeping the other ventilator variables constant. Lessard *et al.*¹⁴ also observed a lower PaO_2 with PC-IRV compared with conventional ventilation with PEEP. Similarly, these authors did not find a significant change in cardiac output with PC-IRV. Mercat *et al.*¹³ and Lessard *et al.*¹⁴ used higher levels of PEEP_t than in the present study, namely from 11 to 14 cmH₂O. This, however, indicates that our negative results with IRV cannot be attributed to insufficient PEEP_t.⁶ We cannot compare our results obtained with inverse I:E ratio ventilation with those of most previous studies because of lack of information on the level of PEEP_t used due to uncontrolled modifications in the ventilator settings after implementation of IRV. Clearly, we cannot exclude the possibility that different effects of PC-IRV may be found

GAS EXCHANGE DURING INVERSE I:E RATIO VENTILATION

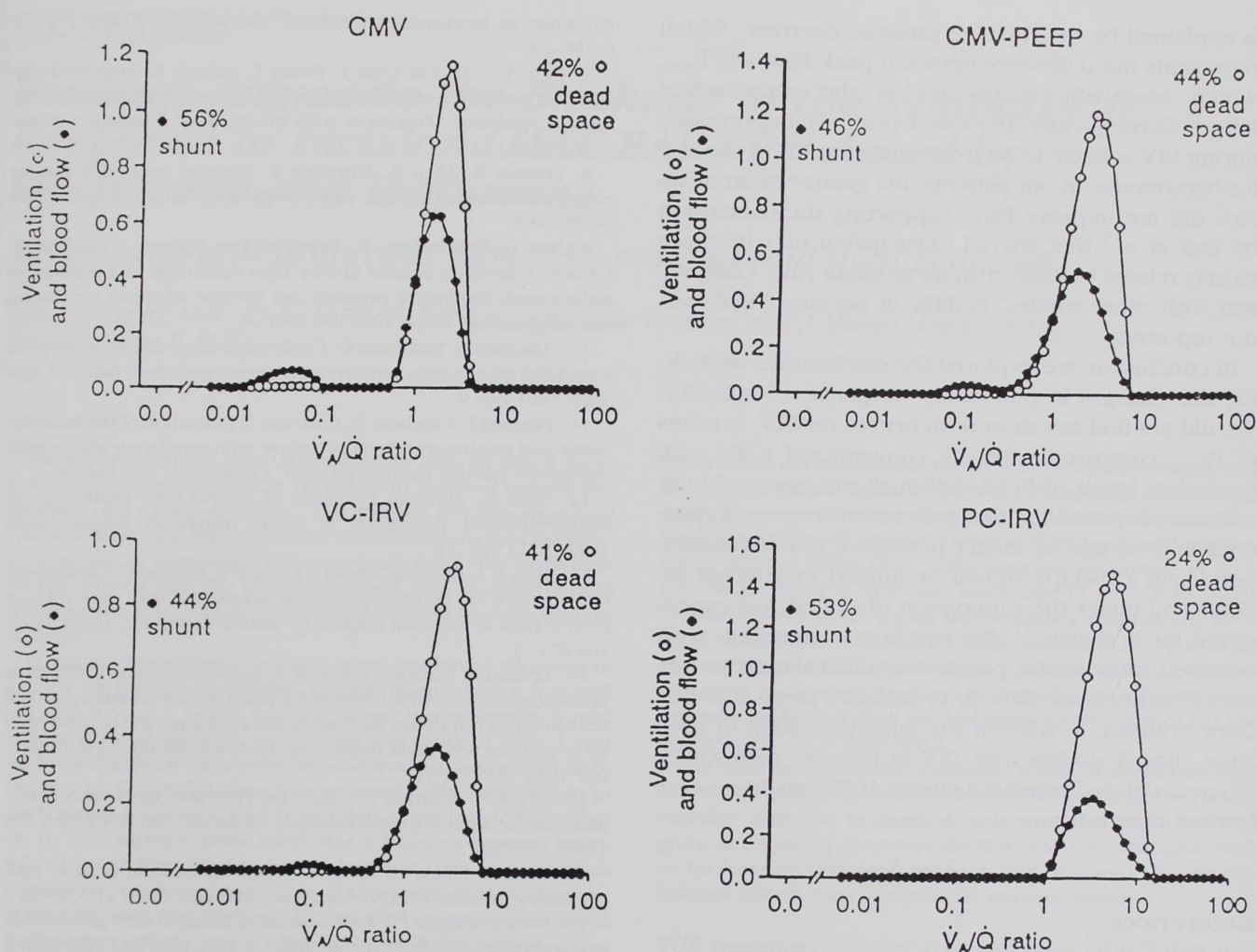


Fig. 1. Ventilation-perfusion (\dot{V}_A/\dot{Q}) distributions with the four ventilatory modes in a representative patient with acute respiratory distress syndrome.

in more severely hypoxemic patients who cannot be adequately ventilated with the conventional modes. A potential critique of the present and previous well-controlled studies^{13,14} pertains to the relatively short duration of the different ventilation modes. Indeed, although it is evident that PC-IRV does not provide any short-term benefit over traditional CMV with PEEP, it cannot be excluded that a longer period of its application may lead to a different result. However, it has been shown that most of the PaO_2 improvement occurs within minutes of the increase in the end-expiratory pressure,²⁰ although in some patients with ARDS PaO_2 might continue to improve for hours after implementation of IRV. Such time-dependent effect, however, was not detected

in a controlled study in which PC-IRV was applied for 24 h.⁵ In contrast to the data reported by Sydow *et al.*²¹ it has been suggested that oxygenation could improve after 8 h with VC-IRV. However, that study dealt mainly with mean Paw release and cannot be considered conclusive in terms of the effects of IRV on pulmonary gas exchange. We believe that this question, as well as the related question regarding the cardiovascular effects of prolonged application of IRV, should be answered before planning large-scale clinical studies with IRV.

The inspiratory flow rate and, consequently, peak Paw were lower in IRV than in CMV-PEEP. The lack of differences in P_{plat} between these ventilatory modalities (IRV and CMV-PEEP), despite the differences in peak Paw ,

is explained by the resistive pressure decrease, which represents the difference between peak P_{aw} and P_{plat} , which essentially occurs within the endotracheal tube.²² Consequently, the lower peak cycling pressure during IRV is likely to be irrelevant in terms of the risk for barotrauma. In our patients, the greater mean P_{aw} did not improve Pa_{O_2} , supporting the conclusion by East *et al.*⁵ that arterial oxygenation may be more closely related to $PEEP_t$ than mean P_{aw} . Comparison with other studies⁴ is difficult because $PEEP_t$ was not reported.

In conclusion, we explored the mechanisms underlying the changes in pulmonary oxygenation with IRV. We did not find any short-term benefit for IRV, in terms of Pa_{O_2} , compared with the conventional CMV with equivalent levels of $PEEP$. Although our results do not rule out the possibility that patients with severe hypoxemia may benefit by longer periods of IRV administration, such a therapy should be limited to selected patients and under the supervision of skilled and experienced medical staff.^{5,12} Because large controlled, well-designed, randomized, prospective clinical trials in critically ill patients are difficult to perform, there is insufficient evidence to warrant the implementation of such large clinical studies with IRV in patients with ARDS, whereas delayed beneficial effects of IRV might deserve further investigation.

References

- Slutsky A: Consensus conference on mechanical ventilation. Part I. Intensive Care Med 1994; 20:64-79
- Bernard G, Artigas A, Brighman K, Carlet J, Falke K, Hudson L, Lamy M, Legall J, Morris A, Spragg R: The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med 1994; 149:818-24
- Marcy TW, Marini JJ: Inverse ratio ventilation in ARDS. Rationale and implementation. Chest 1991; 100:494-504
- Gattinoni L, Marcolin R, Caspani M, Fumagalli R, Mascheroni D, Pesenti A: Constant mean airway pressure with different patterns of positive pressure breathing during the adult respiratory distress syndrome. Bull Eur Physiopathol Respir 1985; 21:275-9
- East T, Bohm S, Wallace J, Clemmer T, Weaver L, Orme J, Morris A: A successful computerized protocol for clinical management of pressure control inverse ratio ventilation in ARDS patients. Chest 1992; 101:697-710
- Brandolese R, Broseghini C, Polese G, Bernasconi M, Brandi G, Milic-Emili J, Rossi A: Effects of intrinsic $PEEP$ on pulmonary gas exchange in mechanically-ventilated patients. Eur Respir J 1992; 6:358-63
- Gurevitch M, Van Dyke J, Young E, Jackson K: Improved oxygenation and lower peak airway pressure in severe adult respiratory distress syndrome. Treatment with inverse ratio ventilation. Chest 1986; 89:211-3
- Tharratt R, Allen R, Albertson T: Pressure controlled inverse ratio ventilation in severe adult respiratory failure. Chest 1988; 94:755-62
- Lain D, DiBenedetto R, Morris S, Van Nguyen A, Saulters R, Causey D: Pressure control inverse ratio ventilation as a method to reduce peak inspiratory pressure and provide adequate ventilation and oxygenation. Chest 1989; 95:1081-8
- Abraham E, Yoshihara G: Cardiorespiratory effects of pressure controlled inverse ratio ventilation in severe respiratory failure. Chest 1989; 96:1356-9
- Poelaert J, Vogelaers D, Colardyn F: Evaluation of the hemodynamic and respiratory effects of inverse ratio ventilation with a right ventricular ejection fraction catheter. Chest 1991; 99:1444-50
- Chan K, Abraham E: Effects of inverse ratio ventilation on cardiorespiratory parameters in severe respiratory failure. Chest 1992; 102:1556-61
- Mercat A, Graini L, Teboul J, Lenique F, Richard C: Cardiorespiratory effects of pressure-controlled ventilation with and without inverse ratio in the adult respiratory distress syndrome. Chest 1993; 104:871-5
- Lessard M, Guérot E, Lorino H, Lemaire F, Brochard L: Effects of pressure-controlled with different I:E ratios versus volume-controlled ventilation on respiratory mechanics, gas exchange, and hemodynamics in patients with adult respiratory distress syndrome. ANESTHESIOLOGY 1994; 80:983-91
- Murray JF, Matthay MA, Luce JM, Flick MR: An expanded definition of the adult respiratory distress syndrome. Am Rev Respir Dis 1988; 138:720-3
- Rossi A, Polese G, Brandi G, Conti G: Intrinsic positive end-expiratory pressure ($PEEP_i$). Intensive Care Med 1995; 21:522-36
- Roca J, Wagner PD: Contribution of multiple inert gas elimination technique to pulmonary medicine. 1: Principles and information content of the multiple inert gas elimination technique. Thorax 1993; 49:815-24
- Rossi A, Santos C, Roca J, Torres A, Féliz MA, Rodríguez-Roisin R: Effects of $PEEP$ on VA/Q mismatching in ventilated patients with chronic airflow obstruction. Am J Respir Crit Care Med 1994; 149:1077-84
- Dantzker DR, Brook L, DeHart P, Lynch J, Weg J: Ventilation-perfusion distribution in the adult respiratory distress syndrome. Am Rev Respir Dis 1979; 120:1039-52
- Katz J, Ozanne G, Zinn S, Fairley H: Time course and mechanisms of lung-volume increase with $PEEP$ in acute pulmonary failure. ANESTHESIOLOGY 1981; 54:9-16
- Sydow M, Burchardi H, Ephraim E, Zielmann S, Crozier T: Long-term effects of two different ventilatory modes on oxygenation in acute lung injury. Am J Respir Crit Care Med 1994; 149:1550-6
- Pesenti A, Pelosi P, Rossi A: The effects of positive-end expiratory pressure in patients with the adult respiratory distress syndrome and in normal anesthetized subjects. Am Rev Respir Dis 1991; 144:101-7