Effects of Inverse Ratio Ventilation versus Positive End-expiratory Pressure on Gas Exchange and Gastric Intramucosal P_{CO_2} and pH under Constant Mean Airway Pressure in Acute Respiratory Distress Syndrome

Chung-Chi Huang, M.D., Mei-Ju Shih, M.S.N., R.N., R.T.,† Ying-Huang Tsai, M.D.,‡ Yu-Chen Chang, B.S.N., R.N.,§ Thomas C. Y. Tsao, M.D.,‖ Kuang-Hung Hsu, Ph.D.#*

Background: In patients with acute respiratory distress syndrome, whether inverse ratio ventilation differs from high positive end-expiratory pressure (PEEP) for gas exchange under a similar mean airway pressure has not been adequately examined. The authors used arterial oxygenation, gastric intramucosal partial pressure of carbon dioxide (P_{iCO_2}), and pH (pHi) to assess whether pressure-controlled inverse ratio ventilation (PC-IRV) offers more benefits than pressure-controlled ventilation (PCV) with PEEP.

Methods: Seventeen acute respiratory distress syndrome patients were enrolled and underwent mechanical ventilation with a PCV inspiratory-to-expiratory ratio of 1:2, followed by PC-IRV 1:1 initially. Then, they were randomly assigned to receive PC-IRV 2:1, then 4:1 or 4:1, and then 2:1, alternately. The baseline setting of PCV 1:2 was repeated between the settings of PC-IRV 2:1 and 4:1. Mean airway pressure and tidal volume were kept constant by adjusting the levels of peak inspiratory pressure and applied PEEP. In each ventilatory mode, hemodynamics, pulmonary mechanics, arterial and mixed venous blood gas analysis, P_{iCO_2}, and pHi were measured after a 1-h period of stabilization.

Results: With a constant mean airway pressure, PC-IRV 2:1 and 4:1 decreased arterial and mixed venous oxygenation as compared with baseline PCV 1:2. Neither the global oxygenation indices with oxygen delivery and uptake nor P_{iCO_2} and pHi were improved by PC-IRV. During PC-IRV, applied PEEP was lower, and auto-PEEP was higher.

Conclusion: When substituting inverse ratio ventilation for applied PEEP to keep mean airway pressure constant, PC-IRV does not contribute more to better gas exchange and gastric intramucosal P_{iCO_2} and pHi than does PCV 1:2 for acute respiratory distress syndrome patients, regardless of the inspiratory-to-expiratory ratios.

RECENTLY, inverse inspiratory-to-expiratory (I:E) ratio ventilation (IRV) has been used increasingly as an alternative therapeutic option for acute respiratory distress syndrome (ARDS) patients to improve arterial oxygenation and lower the risk of barotrauma[1-3] when conventional ratio ventilation with positive end-expiratory pressure (PEEP) has been judged inadequate. However, IRV remains a controversial ventilatory method.[4,5] Recently published studies do not find advantages for IRV over conventional I:E ratio ventilation with PEEP in terms of lung mechanics and oxygenation when the end-expiratory pressures are kept constant.[6-10]

Mean airway pressure (MAP) is a major determinant of oxygenation and hemodynamic compromise during mechanical ventilation.[1,11,12] Oxygen delivery ($\dot{D}_{O_2}$) was reported as a critical prognostic factor for ARDS[13]; therefore, the optimal MAP should be the pressure that can provide maximal $\dot{D}_{O_2}$. Nonetheless, whether the different methods for achieving a similar MAP (such as high-level PEEP or IRV) differ with respect to risks and benefits remained controversial, even in the consensus conference on ARDS.[14]

Multiple systems organ failure, rather than respiratory insufficiency, is the main cause of death for ARDS.[13] Monitoring and maintaining adequate tissue oxygenation is necessary to ensure organ function, survival, and repair. However, global indices of oxygen delivery and consumption ($\dot{V}_{O_2}$) may not provide reliable information on the adequacy of tissue oxygenation.[15] Monitoring of gastric intramucosal partial pressure of carbon dioxide (P_{iCO_2}) and pH (pHi) by gastric tonometry provide quantitative information about the adequacy of splanchnic oxygenation. Recently, P_{iCO_2} and pHi have been suggested as predictors for the development of multiple systems organ failure and survival in patients of trauma or sepsis.[16-18] P_{iCO_2} and pHi are also used as indices to judge the effectiveness of therapeutic interventions, or as end points to guide resuscitation.[16,17]

This goal of this study is to investigate, under constant MAP, whether substituting IRV for applied PEEP has any physiologic advantage. We hypothesized that if the MAP has been set to achieve maximal $\dot{D}_{O_2}$ by titrating the level of applied PEEP and has been kept constant, pressure-controlled inverse ratio ventilation (PC-IRV) with various inverse I:E ratios offers no more benefit than pressure-controlled ventilation (PCV) 1:2 with applied PEEP for gas exchange and P_{iCO_2} and pHi.

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* Assistant Professor, Division of Pulmonary and Critical Care Medicine, Chang Gung Memorial Hospital. Assistant Professor, Department of Respiratory Care, Chang Gung University, Tao-Yuan, Taiwan. † Instructor, Department of Respiratory Care, # Associate Professor, Department of Health Care Management, Chang Gung University. ‡ Attending Physician, Division of Pulmonary and Critical Care Medicine, Chang Gung Memorial Hospital. Assisant Professor, Department of Respiratory Care, Chang Gung University. § Registered Nurse, ‖ Associate Professor, Division of Pulmonary and Critical Care Medicine, Chang Gung Memorial Hospital.

Address reprint requests to Dr. Tsai: Division of Pulmonary and Critical Care Medicine, Chang Gung Memorial Hospital, 5, Fu-Hsin St. Kweishan, Tao-Yuan, 333 Taiwan. Address electronic mail to: chestmed@adm.cgmh.org.tw. Individual article reprints may be purchased through the Journal Web site, www.anesthesiology.org.

Materials and Methods

Patients

The study was approved by the Institutional Review Board for Human Research of Chang Gung Memorial Hospital (Taoyuan, Taiwan). Informed written consent was obtained from the nearest relative, who had been given a full explanation of the study. A total of 17 ARDS patients with a lung injury score[19] greater than 2.5 (age, 57 ± 21 y [mean ± SD]; range, 23–90 y; 9 men, 8 women) who were admitted to the medical intensive care unit were enrolled. Criteria for inclusion were as follows: (1) acute onset lung injury, (2) arterial oxygen tension/fraction of inspired oxygen (Pao$_2$/Fio$_2$) ≤ 200 mmHg, (3) bilateral infiltrates seen on the frontal chest radiograph, and (4) pulmonary wedge pressure ≤ 18 mmHg.[20] Only patients whose hemodynamics were judged to be clinically stable were enrolled, although vasoactive drugs, such as dopamine and norepinephrine, were still needed in 14 of the 17 patients. All the patients were observed early in the course of ARDS. The duration from diagnosis of ARDS to the time of study was 2.5 ± 1 days.

Measurements

Hemodynamic and Cardiac Output. Hemodynamics, including systolic arterial pressure, mean systemic arterial pressure, pulmonary arterial pressure, central venous pressure, and heart rate, during the time of blood gas sampling were recorded from an on-line HP Component Monitoring System (model 56S, M 1165A; Hewlett-Packard, Boblingen, Germany). The cardiac output computer (Vigilance Monitor; Baxter Edwards Critical Care, Irvine, CA) used in this study, along with the pulmonary artery catheter (IntelliCath, 7.5-French; Baxter Edwards Critical Care), could monitor cardiac output automatically and continuously using thermodilution principles and stochastic system identification techniques. The displayed value during blood gas sampling was recorded to represent the cardiac output at the time of that blood gas analysis.

Blood Gas Analysis. Arterial and mixed venous blood gas samples were obtained simultaneously from the arterial cannula and pulmonary artery catheter at the end of each ventilatory setting, and kept anaerobically for analysis with a blood gas analyzer (Corning 178; Ciba Corning Diagnostic Corp., Medfield, MA) as soon as possible. $\dot{D}o_2$ and $\dot{V}o_2$ were calculated as

$$\text{cardiac output} \times \text{Cao}_2 \times 10,$$

and

$$\text{cardiac output} \times (\text{Cao}_2 - \text{Cvo}_2) \times 10,$$

respectively. The venous admixture (Q$_S$/Q$_T$) was calculated as

$$Q_S/Q_T = (Cc'o_2 - Cao_2)/(Cc'o_2 - Cvo_2).$$

Cao$_2$ and Cvo$_2$ represent the oxygen content of the systemic artery and mixed venous blood, respectively, and were calculated as

$$\{[\text{hemoglobin (g/100 ml)} \times 1.36 \times (\text{Sao}_2 \text{ or } \text{Svo}_2)]$$
$$+ 0.003 \times (\text{Pao}_2 \text{ or } \text{Pvo}_2)\}.$$

Cc'o$_2$ represents the oxygen content of end-capillary blood and was derived from the same equation. Capillary oxygen partial pressure (Pc'o$_2$) was assumed to be equal to the alveolar oxygen partial pressure (PAo$_2$).

Pico$_2$ and pHi. A gastric tonometer catheter (TRIP NGS catheter; Tonometrics, Inc. Worcester, MA) was inserted into the stomach *via* the nasogastric route. Correct positioning of the catheters in the stomach was confirmed radiographically and by an auscultation of injected air over the epigastrium. The tonometer catheter was connected to an automated gas analyzer (Tonocap; Datex, Helsinki, Finland). The Tonocap monitor automatically fills the tonometer balloon with 5 ml room air, which is then kept in the catheter to allow carbon dioxide diffusion. After a preset equilibration time of 15 min (default), the system automatically aspirates the air sample from the catheter and measures partial pressure of carbon dioxide (Pco$_2$) with an infrared sensor. The Tonocap monitor calculates the pHi from the arterial carbon dioxide tension (Paco$_2$) and arterial pH (pHa) entered by the user and the latest Pico$_2$ value measured, using the following formula:

$$\text{pHi} = \text{pHa} + \log_{10}(\text{Paco}_2/\text{Pico}_2).$$

The air is then recycled into the catheter balloon to avoid carbon dioxide depletion in the catheter system. The entire sequence of filling, aspiration, Pico$_2$ measurement, and reinflation is fully automated.[21]

Pulmonary Mechanics. Airway pressure, flow, and esophageal pressure were continuously measured using a Bicore CP-100 pulmonary mechanics monitor (Bicore, Irvine, CA). The pressure transducer with pneumotachograph (VarFlex Flow Transducer; Bicore, Irvine, CA) was placed between the Y piece and the endotracheal tube. Peak and mean airway pressures were breath-by-breath and were continuously displayed by the Bicore CP-100 monitor. The proper position of the esophageal balloon (SmartCath Esophageal Balloon Catheter; Bicore, Irvine, CA) in the mid esophagus was confirmed radiographically and by cardiac oscillations observed on the esophageal pressure tracing.[22] The Bicore CP-100 monitor automatically filled the balloon with 0.8 ml air and performed a leakage test. Tidal volume (V$_T$) was obtained by numerical integration of the inspiratory flow signal. Minute ventilation and respiratory rate were electronically analyzed and calculated from the flow signal. End-inspiratory plateau and end-expiratory plateau pressures were established by activating the inspiratory or expiratory hold on the Servo 300 ventilator (Servo 300 venti-

lator; Siemens-Elema, Solna, Sweden) for 5 s. These occlusion maneuvers were repeated 3–5 times, leaving five regular mechanical ventilatory cycles in between. Auto-PEEP was defined as the difference between total PEEP and applied PEEP. All the digital parameters derived from the Bicore CP-100 were recorded continuously, breath-by-breath, and were stored in a personal computer in the spreadsheet form for 5 min at the end of each ventilatory setting. To eliminate probable spontaneous variation, the mean values of these breaths were used to represent the ventilatory status of that period.

Study Design

All patients were sedated with a continuous infusion of midazolam (F. Hoffmann-La Roche Ltd., Basle, Switzerland), propofol (ICI Pharmaceuticals, Cheshire, England), or both and were paralyzed with atracurium (F H Faulding & Co. Ltd., Victoria, Australia) to avoid muscular activity during the study. They were ventilated at a rate of 20 breaths/min with a Servo 300 ventilator (Siemens-Elema). The inspiratory pressure was set to deliver a V_T of 6–8 ml/kg. To determine the optimal level of MAP, we adjusted the level of applied PEEP from the original setting by an increment of 2–3 cm H_2O each time. According to the recommendation of Patel and Singer,[23] $\dot{D}o_2$ was measured 15 min after each increase of applied PEEP. The level of PEEP was increased gradually until $\dot{D}o_2$ reached a plateau or even decreased. The MAP at the PEEP level with the highest $\dot{D}o_2$ was regarded as the optimal MAP. The optimal MAP and V_T were held constant by adjusting the levels of peak inspiratory pressure and applied PEEP after each change of I:E ratio. F_{IO_2} was kept the same as its previous use before entry into the study and ranged from 40 to 100%.

The study comprised five ventilatory settings of 60 min each. The initial ventilatory mode was the PCV with a conventional I:E of 1:2. The ventilatory setting was then shifted to PC-IRV 1:1. We anticipated that the dynamic hyperinflation and auto-PEEP might become greater and that the hemodynamic compromise would become more severe after the I:E ratio became greater than 1:1. Therefore, after the low-grade inverse of I:E 1:1, patients were randomized to receive PC-IRV 2:1, then 4:1 or 4:1, and then 2:1, alternately. To eliminate the probable sustained IRV effects from the previous mode, the baseline setting PCV 1:2 was repeated between settings of PC-IRV 2:1 and 4:1. The sequence of the ventilatory settings, as a result, was either sequence A: baseline PCV 1:2 (1) → PC-IRV 1:1 → PC-IRV 2:1 → baseline PCV 1:2 (2) → PC-IRV 4:1; or sequence B: baseline PCV 1:2 (1) → PC-IRV 1:1 → PC-IRV 4:1 → baseline PCV 1:2 (2) → PC-IRV 2:1. In each ventilatory mode, measurements of hemodynamics, pulmonary mechanics, arterial and mixed venous blood gas analysis, P_{ICO_2}, and pHi were performed after a 1-h period of stabilization. The rates of intravenous fluid and vasopressor infusion were kept fixed during the study periods. Endo-

tracheal suctioning was performed only after the recording of the investigated parameters.

Statistical Analysis

The results obtained are expressed as mean ± SD. A *P* value less than 0.05 was considered significant. The 95% confidence interval[24] of the difference between data from each of the three PC-IRV settings and its previous baseline PCV 1:2 (Δ1:1, Δ2:1, Δ4:1) is calculated to compare the effects of PC-IRV with PCV 1:2. The Δ1:1 represents the difference between PC-IRV 1:1 and baseline PCV 1:2 (1). The Δ2:1 represents the difference between PC-IRV 2:1 with baseline PCV 1:2 (1) for patients with sequence A and the difference between PC-IRV 2:1 with baseline PCV 1:2 (2) for patients with sequence B. On the contrary, Δ4:1 represents the difference between PC-IRV 4:1 with baseline PCV 1:2 (2) for patients with sequence A and the difference between PC-IRV 4:1 with baseline PCV 1:2 (1) for patients with sequence B. The 95% confidence interval represents the range between mean ± ($t_{1-\alpha/2} \times SD/\sqrt{n}$), where $t_{1-\alpha/2}$ is the appropriate value from the *t* distribution with n − 1 degrees of freedom associated with a confidence of $100 \times (1-\alpha)\%$. A zero difference outside the 95% confidence interval indicated that a statistically significant difference existed between the setting of PC-IRV with its previous baseline PCV 1:2 at the 5% level.

Results

Table 1 summarizes the main characteristics of the patients. The severity of ARDS expressed as lung injury score was 3.2 ± 0.4 (range, 2.5–3.75). The mean APACHE III score at the time of diagnosing ARDS was 74 ± 26 (range, 42–120). Eight cases were studied with sequence A, and nine cases were studied with sequence B. The initial applied PEEP level set to achieve the optimal MAP was 14.5 ± 2.8 cm H_2O (range, 10–20 cm H_2O). In case 6, the exact values of P_{ICO_2} measured were too high in all settings of PC-IRV, higher than the upper limit (112 mmHg) displayed by the Tonocap monitor. Therefore, only 16 cases were studied in the comparisons of pHi and P_{ICO_2}. All patients completed the study uneventfully.

Hemodynamics

With the MAP kept constant, PC-IRV did not compromise the hemodynamics, regardless of the degree of IRV (table 2). There were no significant changes in cardiac output, heart rate, systolic and mean arterial pressures, central venous pressure, and pulmonary capillary wedge pressure throughout the study. Systemic and pulmonary vascular resistance were stable, as well. The systolic and mean pulmonary arterial pressures during PC-IRV 4:1

Table 1. Patient Characteristics

Patient	Age	Gender	ALIS	APACHE III	PCWP (cm H_2O)	Pa_{O_2}/F_{IO_2} (mmHg)	Outcome	Diagnosis
1	67	M	3.25	95	7	130	Died	Pneumonia, acute renal failure
2	85	M	3.25	54	13	155	Died	Pneumonia
3	42	M	2.5	69	7	160	Died	Pneumonia, liver cirrhosis
4	68	F	3.5	123	8	80	Died	Septic shock, UTI, renal failure
5	39	F	3.75	51	18	84	Died	Pneumonia, Hodgkin disease
6	54	M	3.25	67	13	77	Died	Pneumonia, septic shock
7	63	M	3	69	10	129	Died	Pneumonia, diabetes mellitus
8	68	F	2.75	80	10	142	Died	Pneumonia, septic shock
9	27	F	2.5	45	12	83	Alive	Pneumonia
10	90	M	3	88	17	184	Alive	Pneumonia, UTI, septic shock
11	31	M	3.5	103	16	77	Died	Acute pancreatitis, renal failure
12	51	F	3.25	58	6	50	Alive	Pneumonia, thrombocytopenia
13	23	F	3	130	9	122	Died	Pneumonia, SLE
14	78	M	3.5	71	14	58	Alive	Septic shock
15	52	F	3.5	42	14	90	Died	Pneumonia
16	54	F	3.5	55	14	70	Alive	Pneumonia, breast cancer
17	83	M	3	57	12	133	Died	Pneumonia

ALIS = acute lung injury score; APACHE = acute physiology and chronic health evaluation; PCWP = pulmonary capillary wedge pressure; Pa_{O_2}/F_{IO_2} = Pa_{O_2}/F_{IO_2} at the time of diagnosis of ARDS; UTI = urinary tract infection; SLE = systemic lupus eryethematosis; ARDS = adult respiratory distress syndrome.

were greater than those during baseline PCV 1:2, but the differences were small.

Gas Exchange

Arterial and mixed venous blood gases analysis, global oxygenation indices of $\dot{D}_{O_2}$ and $\dot{V}_{O_2}$, and regional oxygenation index of P_{ICO_2} and pHi during ventilation with all the various I:E ratios are listed in table 3. PC-IRV 2:1 and 4:1 significantly worsened both Pa_{O_2} and mixed venous oxygen tension (Pv_{O_2}) as compared with its previous baseline PCV 1:2. Q_S/Q_T during PC-IRV 4:1 was slightly higher than during PCV 1:2. $\dot{D}_{O_2}$ and $\dot{V}_{O_2}$ remained stationary after shifting the mode to PC-IRV. The high-grade IRV (2:1 and 4:1) resulted in a significant increase in pHa and decreases in Pa_{CO_2}, Pv_{CO_2}, and bicarbonate (HCO_3^-). Despite the

changes in pHa, Pa_{CO_2}, and HCO_3^-, P_{ICO_2} and pHi remained unchanged across all five settings. The gastric intramucosal–arterial P_{CO_2} gradient (P_{ICO_2}–Pa_{CO_2}) during PC-IRV 1:1 is greater than the P_{ICO_2}–Pa_{CO_2} gradient during PCV 1:2.

Pulmonary Mechanics

In keeping with the study design, MAP, V_T, and minute ventilation were kept similar. PC-IRV resulted in a progressively greater reduction in peak inspiratory pressure than did the previous baseline PCV 1:2. Auto-PEEP augmented gradually with the extension of inspiratory time. To maintain MAP at a constant level, the applied PEEP and total PEEP levels needed to be reduced accordingly after shifting the ventilator to PC-IRV.

Table 2. Hemodynamic Data for Each Ventilatory Setting

Variable	Δ 1:1	Δ 2:1	Δ 4:1	Baseline PCV 1:2 (1)	Baseline PCV 1:2 (2)	PC-IRV 1:1	PC-IRV 2:1	PC-IRV 4:1
CO ($l \cdot min^{-1} \cdot m^{-2}$)	−0.02 ± 0.45	−0.10 ± 0.44	−0.01 ± 0.50	3.64 ± 1.22	3.69 ± 1.23	3.62 ± 1.17	3.60 ± 1.28	3.63 ± 1.13
HR (beats/min)	0 ± 7	−1 ± 8	2 ± 4	119 ± 24	117 ± 23	119 ± 24	117 ± 25	120 ± 23
ABPs (mmHg)	−1 ± 10	8 ± 20	3 ± 11	117 ± 22	117 ± 20	115 ± 22	122 ± 26	123 ± 28
ABPm (mmHg)	−1 ± 7	4 ± 10	1 ± 6	83 ± 15	82 ± 14	82 ± 16	85 ± 17	85 ± 16
PAPs (mmHg)	0 ± 4	1 ± 5	2 ± 3§	40 ± 9	39 ± 8	40 ± 9	41 ± 9	41 ± 10
PAPm (mmHg)	0 ± 3	1 ± 3	2 ± 3§	29 ± 6	28 ± 5	29 ± 5	30 ± 6	30 ± 6
PCWP (mmHg)	0 ± 1.3	0 ± 2.7	1 ± 1.9	12 ± 4.3	12 ± 3.5	12 ± 3.7	12 ± 4.1	13 ± 4.7
CVP (mmHg)	0 ± 0.9	0 ± 1.3	0 ± 1.2	11 ± 4.1	11 ± 4.0	10 ± 3.8	11 ± 4.2	11 ± 3.8
SVRI ($dyn \cdot s^{-1} \cdot cm^{-5} \cdot m^{-2}$)	−32 ± 377	130 ± 314	70 ± 214	1,704 ± 621	1,708 ± 589	1,671 ± 791	1,813 ± 698	1,798 ± 583
PVRI ($dyn \cdot s^{-1} \cdot cm^{-5} \cdot m^{-2}$)	7 ± 64	18 ± 103	43 ± 86	410 ± 178	403 ± 154	417 ± 145	447 ± 172	426 ± 181

Values are mean ± SD. Δ 1:1 represents the difference between PC-IRV 1:1 and baseline PCV 1:2 (1). Δ 2:1 represents the difference between PC-IRV 2:1 with baseline PCV 1:2 (1) for patients with sequence A, and difference between PC-IRV 2:1 with baseline PCV 1:2 (2) for patients with sequence B. Δ 4:1 represents the difference between PC-IRV 4:1 with baseline PCV 1:2 (2) for patients with sequence A, and difference between PC-IRV 4:1 with baseline PCV 1:2 (1) for patients with sequence B.

CO = cardiac output; HR = heart rate; ABPs = systolic arterial pressure; ABPm = mean arterial pressure; PAPs = systolic pulmonary arterial pressure; PAPm = mean pulmonary arterial pressure; PCWP = pulmonary capillary wedge pressure; CVP = central venous pressure; SVRI = systemic vascular resistance index; PVRI = pulmonary vascular resistance index.

Table 3. Arterial and Mixed Venous Blood Gases, Venous Admixture, Gastric Intramucosal P_{CO_2} and pH Data for Each Ventilatory Setting

Variable	Δ 1:1	Δ 2:1	Δ 4:1	Baseline PCV 1:2 (1)	Baseline PCV 1:2 (2)	PC-IRV 1:1	PC-IRV 2:1	PC-IRV 4:1
Pa_{O_2} (mmHg)	−8.6 ± 18.4	−10.3 ± 19.0*	−17.5 ± 22.9*	116 ± 52.2	125 ± 56.3	107 ± 40.3	108 ± 49.4	104 ± 39.3
Pa_{CO_2} (mmHg)	−2.9 ± 5.8	−4.1 ± 4.2*	−3.4 ± 5.6*	44 ± 12.5	41 ± 11.3	41 ± 8.5	38 ± 8.8	39 ± 8.7
pHa	0.01 ± 0.03	0.03 ± 0.03*	0.03 ± 0.03*	7.37 ± 0.14	7.37 ± 0.14	7.38 ± 0.14	7.39 ± 0.14	7.4 ± 0.13
Pv_{O_2} (mmHg)	0.1 ± 4.2	−2.9 ± 2.8*	−2.2 ± 3.7*	39 ± 5.3	40 ± 7.4	39 ± 5.4	37 ± 6.3	37 ± 4.7
Sv_{O_2} (%)	0.6 ± 5.2	−3.1 ± 4.2*	−2.1 ± 5.3	69.6 ± 7.4	70.5 ± 8.2	70.2 ± 8.5	67.4 ± 9.6	67.6 ± 8.6
Pv_{CO_2} (mmHg)	−1.3 ± 3.6	−3.8 ± 3.9*	−3.2 ± 4.6*	48 ± 12.5	47 ± 11.8	47 ± 10.3	44 ± 10.0	44 ± 9.7
HCO_3^- (mM)	−0.7 ± 2.0	−1.4 ± 1.9*	−1.0 ± 1.4*	24.7 ± 6.5	25.3 ± 6.6	23.9 ± 6.2	23.5 ± 6.5	24.1 ± 6.5
Pi_{CO_2} (mmHg)	1.3 ± 7.0	−2.3 ± 7.6	−0.3 ± 9.9	60 ± 16.0	61 ± 15.1	61 ± 17.6	57 ± 15.6	61 ± 17.2
pHi	−0.02 ± 0.06	0.00 ± 0.07	−0.01 ± 0.08	7.24 ± 0.16	7.21 ± 0.17	7.22 ± 0.20	7.23 ± 0.20	7.21 ± 0.19
Pi_{CO_2}–Pa_{CO_2} (mmHg)	4.1 ± 7.1*	1.8 ± 8.2	3.3 ± 8.3	16 ± 9.7	19 ± 11.1	20 ± 15.5	18 ± 12.0	22 ± 17.4
Q_S/Q_T (%)	1.3 ± 5.7	0.6 ± 3.1	2.6 ± 4.3*	24.8 ± 11.1	23.4 ± 10.5	26.1 ± 11.7	25.2 ± 11.2	26.1 ± 12.8
$\dot{D}_{O_2}$ (ml · min^{-1} · m^{-2})	−3 ± 59	−18 ± 53	−7 ± 72	451 ± 139	462 ± 144	448 ± 135	443 ± 146	445 ± 137
$\dot{V}_{O_2}$ (ml · min^{-1} · m^{-2})	−5 ± 19	5 ± 18	2 ± 17	126 ± 38	128 ± 43	121 ± 38	131 ± 46	130 ± 40

Values are mean ± SD. Δ 1:1 represents the difference between PC-IRV 1:1 and baseline PCV 1:2 (1). Δ 2:1 represents the difference between PC-IRV 2:1 with baseline PCV 1:2 (1) for patients with sequence A, and difference between PC-IRV 2:1 with baseline PCV 1:2 (2) for patients with sequence B. Δ 4:1 represents the difference between PC-IRV 4:1 with baseline PCV 1:2 (2) for patients with sequence A, and difference between PC-IRV 4:1 with baseline PCV 1:2 (1) for patients with sequence B.

*Zero difference outside the 95% CI, and statistically significant difference between the setting of PC-IRV with its prior baseline PCV 1:2 at the 5% level.

Pi_{CO_2} = gastric intramucosal P_{CO_2}; pHi = gastric intramucosal pH; Pi_{CO_2}–Pa_{CO_2} = gastric intramucosal–arterial P_{CO_2} gradient; pHa–pHi = arterial pH–pHi gradients; Q_S/Q_T = venous admixture; $\dot{D}_{O_2}$ = oxygen delivery; $\dot{V}_{O_2}$ = oxygen uptake.

Discussion

The major findings of this study are that at constant mean airway pressure, PC-IRV did not improve arterial oxygenation, global oxygenation indices ($\dot{D}_{O_2}$ and $\dot{V}_{O_2}$), and gastric intramucosal P_{CO_2} and pH more than did PCV 1:2 with PEEP.

Mean airway pressure, as a clinically measurable reflection of mean alveolar pressure, fundamentally reflects oxygen exchange and cardiovascular performance during conditions of passive inflation.[11,12,14] Excessively high MAP, although improving arterial oxygenation, may decrease cardiac output and jeopardize $\dot{D}_{O_2}$. Consequently, MAP should be increased only sufficiently to accomplish the unequivocal clinical objectives for gas exchange and maximal $\dot{D}_{O_2}$. Recently, in several studies in which IRV was compared with conventional ratio ventilation with similar total PEEP (applied PEEP plus auto-PEEP),[2,6,8,9,25] the increase of MAP after implementation of IRV resulted in a decrease of cardiac output. This may then contribute to a further decrease of $\dot{D}_{O_2}$ and implies that MAP might have been increased to a deleterious level. Therefore, MAP should be kept constant when settling the clinical utility of IRV over applied PEEP.

With MAP kept constant, previous reports comparing IRV with VCV demonstrated no change in cardiac output.[25–27] Similarly, our data showed that cardiac output, arterial blood pressure, and vascular resistance were stationary throughout the study. PC-IRV 4:1 only resulted in small changes in systolic and mean pulmonary artery pressures (table 2). Using applied PEEP or IRV to reach the same MAP exerted the same influences on cardiac output and hemodynamics.

The effects of different I:E ratios on arterial oxygenation might result from the contrasting effects between applied PEEP and auto-PEEP. The amount of applied PEEP adds directly to the level of MAP, whereas during IRV, MAP increases because mean inspiratory pressure increases and because auto-PEEP is created.[11,12] To maintain a constant MAP, the level of applied PEEP after progressive lengthening of inspiratory time must be reduced. On the contrary, auto-PEEP augmented gradually. Although applied PEEP is homogeneously distributed, Kacmarek *et al.*[28] found that a greater maldistribution of local lung unit end-expiratory pressure was established with the auto-PEEP in a four-unit lung model. Because parenchymal involvement in ARDS is heterogeneous, the distribution of auto-PEEP induced by PC-IRV is likely to be uneven because of time constant inequalities between lung units. Therefore, the slowest lung units could still be collapsed while a substantial level of auto-PEEP is measured by the end-expiratory occlusion method. However, the local PEEP for the fast lung units might be inadequate because of the decrease of applied PEEP. Steward *et al.*[29] demonstrated that applied PEEP is more effective in improving Pa_{O_2} than IRV per increment of MAP ($\Delta Pa_{O_2}/\Delta$MAP 6.08 *vs.* 1.90). Pesenti *et al.*[25] disclosed that Pa_{O_2}, with MAP kept constant by extending the inspiratory time, was much decreased when an applied PEEP lower than inflection-point pressure (P_{flex}) was compared with an applied PEEP higher than P_{flex}. Brandolese *et al.*[30] also discovered a more significant improvement in arterial oxygenation with applied PEEP than with auto-PEEP, which they attributed to the less homogeneous distribution of auto-PEEP between lung units with different time constants.

Table 4. Pulmonary Mechanics for Each Ventilatory Setting

Variable	Δ 1:1	Δ 2:1	Δ 4:1	Baseline PCV 1:2 (1)	Baseline PCV 1:2 (2)	PC-IRV 1:1	PC-IRV 2:1	PC-IRV 4:1
PIP (cm H$_2$O)	−4.1 ± 2.1*	−7.0 ± 2.6*	−7.2 ± 4.2*	37.9 ± 7.4	38.2 ± 7.8	33.8 ± 6.2	31.2 ± 6.0	30.7 ± 4.8
MAP (cm H$_2$O)	−0.9 ± 1.9	−1.2 ± 2.3	−0.7 ± 2.4	26.7 ± 5.4	26.5 ± 5.7	25.8 ± 5.4	25.7 ± 5.9	25.6 ± 4.6
V$_T$ (ml)	4 ± 23	−3 ± 21	−7 ± 25	361 ± 50	364 ± 56	358 ± 55	361 ± 55	355 ± 54
V$_E$ (l/min)	−0.12 ± 0.43	−0.10 ± 0.46	−0.14 ± 0.48	7.17 ± 0.99	7.29 ± 1.02	7.05 ± 1.05	7.18 ± 1.08	7.03 ± 1.09
Applied PEEP (cm H$_2$O)	−2.0 ± 0.9*	−4.7 ± 1.7*	−9.0 ± 2.5*	14.5 ± 2.8	14.4 ± 2.9	12.5 ± 2.6	9.8 ± 3.0	5.5 ± 2.8
Total PEEP (cm H$_2$O)	−1.2 ± 0.8*	−2.1 ± 1.2*	−2.3 ± 1.9*	14.7 ± 2.5	14.5 ± 2.8	13.5 ± 2.5	12.5 ± 2.9	12.3 ± 2.7
Auto PEEP (cm H$_2$O)	0.8 ± 1.0*	2.6 ± 1.5*	6.7 ± 3.2*	0.2 ± 0.5	0.1 ± 0.2	0.9 ± 1.0	2.7 ± 1.5	6.8 ± 3.2

Values are mean ± SD. Δ 1:1 represents the difference between PC-IRV 1:1 and baseline PCV 1:2 (1). Δ 2:1 represents the difference between PC-IRV 2:1 with baseline PCV 1:2 (1) for patients with sequence A, and difference between PC-IRV 2:1 with baseline PCV 1:2 (2) for patients with sequence B. Δ 4:1 represents the difference between PC-IRV 4:1 with baseline PCV 1:2 (2) for patients with sequence A, and difference between PC-IRV 4:1 with baseline PCV 1:2 (1) for patients with sequence B.

*Zero difference outside the 95% CI and statistically significant difference between the setting of PC-IRV with its prior baseline PCV 1:2 at the 5% level.

PIP = peak inspiratory pressure; MAP = mean airway pressure; V$_T$ = tidal volume; V$_E$ = minute ventilation.

When comparing the cardiorespiratory effects of PCV with PC-IRV in an acute lung injury animal model, Mang *et al.*[27] adjusted the pressure control level and applied PEEP to maintain a constant V$_T$ and MAP. Their data showed that Pao$_2$, albeit not statistically significant, was lower with PC-IRV 4:1 than with PCV 1:2 (172 ± 69 *vs.* 201 ± 78 mmHg). Performed in ARDS patients, our study corroborated the findings of Mang *et al.*[27] Pao$_2$ and Pvo$_2$ both decreased significantly when the inspiratory time was prolonged to PC-IRV 2:1 and 4:1 (table 3). The decreased applied PEEP levels (table 4), with the accompanying higher Q$_S$/Q$_T$ (table 3), probably accounted for the deterioration of Pao$_2$ with PC-IRV. In accordance with the aforementioned study, under similar MAP, replacing the applied PEEP with auto-PEEP from IRV was detrimental to both arterial and mixed venous oxygenation in ARDS patients.

Extending the inspiratory time enhances the clearance of carbon dioxide. PC-IRV has been found to improve Paco$_2$ more than PCV[2,6] or volume-cycled ventilation with PEEP do.[8] This effect is usually attributed to a decrease in physiologic dead space and an improved mixing of alveolar and bronchial gases. Similarly, PC-IRV 2:1 and 4:1 significantly decreased Paco$_2$ more than PCV 1:2 did.

Gastric Pico$_2$ can increase as a result of respiratory acidosis, *i.e.*, stagnation of carbon dioxide with decreased washout from low mucosal blood flow, or as a result of metabolic acidosis, *i.e.*, buffering of the hydrogen ion (H$^+$) from anaerobic metabolism by HCO$_3^-$.[16] Recently, Elizalde *et al.*[31] demonstrated that impairment of gastric mucosal blood flow underlies the development of intramucosal acidosis in mechanically ventilated patients and contended that the measurement of gastric pHi constituted a method to assess the adequacy of perfusion of the gastrointestinal tract in critically ill patients. Knichwitz *et al.*[32] proved that compromised mesenteric blood flow causes significant metabolic and histologic changes in the gastrointestinal tract and argued that the only parameter of importance is the intraluminal

measurement of intramucosal Pco$_2$ that can reflect isolated mesenteric change. Regardless of the origin of increased Pico$_2$, intramucosal acidosis has been clinically associated with a grave prognosis for intensive care unit patients. Pico$_2$ and pHi have been used as an index to judge the effectiveness of therapeutic interventions.

Inadequate splanchnic perfusion may be caused by decreased total cardiac output, inappropriate distribution of flow between organs, and mismatching of oxygen supply to demand within organs. PEEP has been proved not only to reduce cardiac output,[33] but also to decrease mesenteric and portal blood flow[34-35] and to redistribute the cardiac output away from the splanchnic circulation.[36] Therefore, although beneficial in improving arterial oxygenation, the application of PEEP may contribute to mesenteric ischemia and gastrointestinal failure caused by alteration in regional blood flow. The interrelation between IRV and splanchnic blood flow has not been clearly documented. Under constant MAP and V$_T$, IRV reduced the peak inspiratory pressure and total PEEP needed. However, in this study, we did not detect any significant fluctuation in either Pico$_2$ or pHi during PC-IRV as compared with baseline PCV 1:2 (table 3). Because changes in systemic Pco$_2$ produced by systemic respiratory acidosis or alkalosis directly and rapidly affected Pico$_2$, the difference between Pico$_2$ and Paco$_2$ (Pico$_2$–Paco$_2$) has been suggested to be more informative and to be a more reliable index of gastric mucosal oxygenation than is pHi or Pico$_2$ alone because of the correction for abnormalities in systemic arterial Pco$_2$.[37] Table 3 shows that Pico$_2$–Paco$_2$ in PC-IRV 1:1 was significantly greater than in baseline PCV 1:2 with high PEEP. Instead of improvement, PC-IRV did not mitigate gastric intramucosal acidosis or improve the mucosal hypoperfusion.

In summary, our data do not support the application of IRV as a substitute for applied PEEP to achieve a similar MAP in ARDS patients. If we set MAP to be optimal, *i.e.*, with maximal Ḋo$_2$, by titrating the levels of applied PEEP, PC-IRV does not contribute to better gas exchange

and gastric intramucosal P_{CO_2} and pH than does PCV 1:2 with applied PEEP, regardless of the I:E ratios.

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