Work of Breathing During Lung-Protective Ventilation in Patients With Acute Lung Injury and Acute Respiratory Distress Syndrome: A Comparison Between Volume and Pressure-Regulated Breathing Modes

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BACKGROUND: Pressure-control ventilation (PCV) and pressure-regulated volume-control (PRVC) ventilation are used during lung-protective ventilation because the high, variable, peak inspiratory flow rate ($\dot{V}_I$) may reduce patient work of breathing (WOB) more than the fixed $\dot{V}_I$ of volume-control ventilation (VCV). Patient-triggered breaths during PCV and PRVC may result in excessive tidal volume (V_T) delivery unless the inspiratory pressure is reduced, which in turn may decrease the peak $\dot{V}_I$. We tested whether PCV and PRVC reduce WOB better than VCV with a high, fixed peak $\dot{V}_I$ (75 L/min) while also maintaining a low V_T target. METHODS: Fourteen nonconsecutive patients with acute lung injury or acute respiratory distress syndrome were studied prospectively, using a random presentation of ventilator modes in a crossover, repeated-measures design. A target V_T of 6.4 ± 0.5 mL/kg was set during VCV and PRVC. During PCV the inspiratory pressure was set to achieve the same V_T. WOB and other variables were measured with a pulmonary mechanics monitor (Bicore CP-100). RESULTS: There was a nonsignificant trend toward higher WOB (in J/L) during PCV (1.27 ± 0.58 J/L) and PRVC (1.35 ± 0.60 J/L), compared to VCV (1.09 ± 0.59 J/L). While mean V_T was not statistically different between modes, in 40% of patients, V_T markedly exceeded the lung-protective ventilation target during PRVC and PCV. CONCLUSIONS: During lung-protective ventilation, PCV and PRVC offer no advantage in reducing WOB, compared to VCV with a high flow rate, and in some patients did not allow control of V_T to be as precise. *Key words: acute lung injury, acute respiratory distress syndrome, asynchrony, lung-protective ventilation, mechanical ventilation, tidal volume, work of breathing*. [Respir Care 2005;50(12):1623–1631. © 2005 Daedalus Enterprises]

Introduction

To prevent ventilator-associated injury in patients with acute lung injury (ALI) or the acute respiratory distress syndrome (ARDS), a tidal volume (V_T) of 6–7 mL/kg is recommended.[1] However, dyspnea and ventilator-patient asynchrony commonly occur during lung-protective ventilation (LPV)[2] and may signify increased work of breath-

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Table 1. Patient Demographics at Entrance Into Study

Case	Sex	Age	Diagnosis	C_{RS} (mL/cm H_2O)	C_{CW} (mL/cm H_2O)	PEEP (cm H_2O)	P_{aO_2}/F_{IO_2} (mm Hg)	LIS	MIP (cm H_2O)
1	M	28	ARDS: necrotizing pancreatitis, ACS	26	98	8	290†	2.00	46
2	M	69	ALI: necrotizing pancreatitis, ascites, pleural effusions	41	102	5	276	1.75	50
3	M	40	ARDS: necrotizing pancreatitis, ascites	29	67	10	184	2.75	57
4	M	24	ALI: necrotizing pancreatitis, ascites	24	66	8	229	2.25	92
5	F	39	ARDS: *Pneumocystis carinii* pneumonia, pancreatitis	22	82	10	154	3.00	63
6	F	74	ARDS: burns	22	69	5	161	2.75	75
7	M	53	ALI: trauma, sepsis	77	216	5	288	1.25	59
8	F	36	ARDS: amniotic fluid embolism	37	146	5	185	2.25	25
9	M	39	ARDS: pneumonia, sepsis	14	200*	14	90	3.75	45
10	F	41	ARDS: sepsis	25	93	5	297†	2.00	60
11	M	45	ARDS: multiple trauma, sepsis	20	73	5	250†	2.25	42
12	F	65	ARDS: pancreatitis, ascites	23	99	10	156	2.75	30
13	F	72	ALI: multiple trauma	29	99	5	210	2.25	35
14	M	25	ARDS: trauma	15	112	10	158	3.25	27
Mean ± SD		46 ± 17		29 ± 16	102 ± 41	7.5 ± 2.9	209 ± 64	2.45 ± 0.64	50 ± 19

C_{RS} = respiratory system compliance. C_{CW} = chest wall compliance. PEEP = positive end-expiratory pressure. P_{aO_2}/F_{IO_2} = ratio of arterial partial pressure of oxygen to fraction of inspired oxygen. LIS = lung injury score.[24] MIP = maximum inspiratory pressure (esophageal). ARDS = acute respiratory distress syndrome. ACS = abdominal compartment syndrome. ALI = acute lung injury.
*Normal C_{CW} used as default: unable to achieve passive ventilation (mean ± SD of C_{CW} excludes this patient's data point).
†P_{aO_2}/F_{IO_2} is taken from reference arterial blood gas measurement on the day of study and does not reflect the fact that the patient originally met diagnostic criteria for ARDS (eg, $P_{aO_2}/F_{IO_2} < 200$ mm Hg).

ing (WOB). During volume-control ventilation (VCV), increased patient WOB occurs when either the inspiratory flow rate ($\dot{V}_I$) of the ventilator[3] or the V_T[4,5] is below patient demand. In LPV this may be exacerbated by increased respiratory drive from acute hypercapnia.[1,6] Pressure-regulated modes such as pressure-control ventilation (PCV),[7] pressure-regulated volume-control (PRVC),[8] and volume-assured pressure support[9] ventilation are used to manage patients with ALI/ARDS. PCV and volume-assured pressure support utilize a high peak $\dot{V}_I$ that varies with patient flow demand, and both modes reduce WOB in patients with ALI/ARDS ventilated at a V_T of 10 mL/kg.[7,9]

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During LPV with PCV, patient inspiratory efforts may result in excessive V_T delivery[5] unless the inspiratory pressure is reduced. This in turn may reduce the peak $\dot{V}_I$, thus limiting the mode's effectiveness in reducing patient WOB. Similarly, modeling of simulated patient-triggered ventilation with PRVC found that when V_T delivery exceeded the preset V_T, both the airway pressure (P_{aw}) and peak $\dot{V}_I$ subsequently decreased, resulting in increased simulated WOB.[10] The effects of pressure-regulated modes on V_T delivery, peak $\dot{V}_I$, and WOB in patients undergoing LPV have not been investigated. Previous studies[7,11,12] that used a conventional V_T to compare WOB between pressure-regulated modes and VCV may have been biased because measurements were made at a constant V_T and inspiratory time (T_I) that resulted in an abnormally low peak $\dot{V}_I$ during VCV (< 55 L/min). As an example, MacIntyre et al[13] did not find a significant benefit in treating ventilator-patient asynchrony with a pressure-regulated mode, compared to VCV with the peak $\dot{V}_I$ of approximately 75 L/min. In this study we inquired whether PCV and PRVC reduce patient WOB better than VCV with a fixed peak $\dot{V}_I$ of 75 L/min while also maintaining V_T close to an LPV target.

Methods

Subjects

Fourteen nonconsecutive patients on the general surgery, trauma surgery, and medical services were enrolled into the study (Table 1). Signed, informed consent was obtained from each patient's relative. The study was approved by the Committee on Human Research of the University of California, San Francisco. Enrollment criteria

were to meet the North American-European Consensus Conference definition for ALI or ARDS,[14] and clinical use of a $V_T \leq 8$ mL/kg predicted body weight. All patients were managed clinically with the National Institutes of Health ARDS Network[15] low-V_T protocol, and each patient had previously documented episodes of ventilator-patient asynchrony requiring an increased V_T or increased sedation.

Procedures

Upon enrollment, a Smart Cath (Viasys Healthcare, Palm Springs, California) nasogastric tube with an esophageal balloon was placed in the lower third of the esophagus. The balloon position was manipulated while inspecting the synchrony of the peak esophageal pressure (P_{es}) and P_{aw} deflections. When cardiac artifact was minimized, an occlusion test was performed for position confirmation, using the method described by Baydur et al.[16] All patients were studied in the semi-recumbent position. Peak inspiratory pressure (P_{Imax}) was measured using "Method 1" described by Marini et al,[17] whereby the airway was occluded at end-expiration, allowing no movement of air in either an inspiratory or expiratory direction.

Prior to data collection, relaxed chest-wall compliance curves were constructed using an analysis of 2–5 breaths during a brief period of controlled ventilation at the V_T used clinically for LPV. This was achieved following additional sedation with propofol and transient hyperventilation to suppress spontaneous ventilatory activity. The curves were constructed from esophageal pressure-volume tracings with a counterclockwise movement, a narrow loop, and a rightward rotation of the axis.[7] After patients recovered, central respiratory drive was monitored until the presedation baseline had been achieved.

A Dräger Dura E-2 ventilator (Dräger Medical, Telford, Pennsylvania) was used for all studies. The target V_T was that used clinically for LPV and was between 5.5 and 7.3 mL/kg predicted body weight, measured at the circuit Y adapter. For PCV the P_{aw} change (ΔP_{aw}) was set to achieve the target V_T during VCV when passive chest-wall compliance was measured. However, patient inspiratory efforts during PCV commonly caused the V_T to exceed the target, so that the ΔP_{aw} then was decreased. The final ΔP_{aw} used was the *highest* pressure that at least *transiently* produced the target V_T, and this event marked the beginning of the stabilization period for PCV. The minimum ΔP_{aw} used was 10 cm H_2O above the positive end-expiratory pressure (PEEP) level, regardless of V_T delivery. PEEP and fraction of inspired oxygen (F_{IO_2}) were set according to the National Institutes of Health ARDS Network protocol.[15]

Adjustments were made in each mode to achieve ventilator settings most favorable to reducing patient WOB while attempting to constrain V_T delivery. During VCV a square-wave flow pattern was used, with a peak $\dot{V}_I$ of 75 L/min and a T_I range of 0.50–0.80 s. This was done to minimize the end-inspiratory pause time on the Dräger E-2 ventilator, and also to limit intrinsic PEEP (PEEPi) at rapid respiratory frequencies (f).[18] Likewise, the same T_I range was used during PCV and PRVC to maximize peak $\dot{V}_I$ (eg, by requiring a higher P_{aw} to deliver the same V_T within a shorter T_I). A nonbias flow trigger level of 3 L/min was used in all modes. In both PCV and PRVC the pressure-rise time feature was turned off so that the fastest inspiratory pressure-rise and highest possible peak $\dot{V}_I$ could be achieved.[19] The mandatory f on each mode was set to produce the minute ventilation ($\dot{V}_E$) used during clinical management.

Protocol

The study incorporated a random presentation of PCV, PRVC (Auto-Flow), and VCV in a brief, time-series, crossover design. A blind envelope pull was used to prevent presentation bias. Ten minutes were allowed for adaptation and stabilization of the breathing pattern, and data were collected over the following 10 min. Twenty breaths were used for analysis on each mode. After measurements had been completed on each mode, patients then were given a brief period (1–2 min) of breathing on continuous positive airway pressure (CPAP) at the same end-expiratory pressure used during mechanical ventilation, to measure each patient's spontaneous V_T, peak $\dot{V}_I$, and T_I. This was done to provide a gross estimation of ventilator-to-patient differences in V_T (ΔV_Tvent-pt), peak $\dot{V}_I$ (Δ peak $\dot{V}_I$vent-pt), and T_I (ΔT_Ivent-pt) between modes, and to assess potential relationships to WOB and pressure-time product (PTP). Sedation during the study was controlled by the critical care team managing the patient. All patients received continuous infusions of sedatives and/or analgesics that produced a mean Ramsey score of 4.4 ± 0.7 during the study.[20]

Measurements

Patient and ventilator variables were measured with a pulmonary mechanics monitor that incorporated Campbell diagram software (Bicore CP-100, Viasys Healthcare, Palm Springs, California). The precision and accuracy of this monitor has been previously validated.[21,22] The monitor and transducers were calibrated prior to each study. The Var-Flex (Viasys Healthcare, Palm Springs, California) P_{aw}/flow transducer was placed at the circuit Y adapter so that reported V_T excluded compressible circuit volume. End-tidal carbon dioxide partial pressure (P_{ETCO_2}) was measured at the circuit Y adapter, using a sidestream capnometer (Vital Cap, Oridion, Jerusalem, Israel).

Data collection included total f, inspired V_T, peak $\dot{V}_I$, P_{ETCO_2}, PEEPi, the inspiratory change in P_{es} (ΔP_{es}), PTP, and T_I. Central respiratory drive was measured as the change in P_{es} at 100 ms ($P_{0.1}$) after the onset of inspiration. These variables were collected from two 40-breath printed reports, from which 20 randomly selected breaths were used for analysis. A separate 40-breath report was generated during the CPAP trial, from which 20 randomly selected breaths also were used for analysis. P_{ETCO_2} was recorded at 1-min intervals. Campbell diagram software was used to measure patient WOB in J/L,[21] and 20 consecutive breaths were analyzed. PEEPi was measured dynamically as the difference in P_{es} between the end-expiratory plateau and the pressure measured at the onset of inspiratory flow, minus the trigger sensitivity level measured at the airway (the lowest P_{aw} change from baseline at the onset of flow).[7] ΔP_{es} was measured as the change in P_{es} from the end-expiratory pressure to the most negative pressure achieved during inspiration. PTP was calculated using the method described by Sassoon et al,[23] as the integral of the negative change in P_{es} over T_I. During PCV, PRVC, and VCV, T_I was measured from calibrated scalar flow waveforms as the distance between the upstroke of inspiratory flow (excluding any detectable pre-trigger flow plateau signifying circuit decompression) to just before the beginning of expiratory flow. The lung injury score was calculated by the method of Murray et al.[24]

Derived variables were calculated as follows:

$$\dot{V}_E = V_T \times \text{total f (L/min)} \quad (1)$$

$$\text{Respiratory muscle power in J/min } (\dot{W}) = \dot{V}_E \text{ (L/min)} \times \text{WOB (J/L)} \quad (2)$$

$$T_I \text{ (CPAP)} = [60 \text{ s} \div \text{total f}] \times \text{inspiratory time fraction } (T_I/T_{tot}) \text{ (s)} \quad (3)$$

$$\Delta V_T\text{vent-pt} = \text{ventilator } V_T - \text{inspired } V_T \text{ measured during CPAP} \quad (4)$$

$$\Delta \text{ peak } \dot{V}_I\text{vent-pt} = \text{ventilator peak } \dot{V}_I - \text{peak } \dot{V}_I \text{ measured during CPAP} \quad (5)$$

$$\Delta T_I\text{vent-pt} = \text{ventilator } T_I - T_I \text{ measured during CPAP} \quad (6)$$

Statistical Analysis

When assessed by the Kolmogorov-Smirnov test, data were consistent with a normal distribution so that all data are expressed as mean ± standard deviation. Multiple comparisons were made by repeated-measures analysis of variance and Tukey-Kramer post-tests.[25] Correlation was assessed by Pearson product-moment.[25] Statistical analyses were done using commercially-available software (InStat version 3.0, GraphPad Software, San Diego, California). Results were considered significant when $p < 0.05$.

Table 2. Differences in Patient Work of Breathing and Other Variables During Lung-Protective Ventilation Using Volume-Regulated Modes and Pressure-Regulated Modes

	PRVC	PCV	VCV
WOB (J/L)	1.35 ± 0.60	1.27 ± 0.58	1.09 ± 0.59
PTP (cm H_2O/s/min)	229 ± 116	195 ± 94	180 ± 112
$\dot{W}$ (J/min)	16.4 ± 10.7	15.7 ± 9.0	13.2 ± 8.9
$P_{0.1}$ (cm H_2O)	5.5 ± 3.1	4.4 ± 2.1	4.8 ± 3.1
ΔP_{es} (cm H_2O)	17.0 ± 5.9	14.8 ± 4.1	14.6 ± 6.3
V_T (mL)	418 ± 83	436 ± 106	398 ± 79
V_T (mL/kg)	6.9 ± 1.1	7.2 ± 1.4	6.5 ± 0.7
$\dot{V}_I$ (L/min)	57 ± 14*	61 ± 16	76 ± 5
$\dot{V}_E$ (L/min)	11.6 ± 3.3	12.3 ± 3.6	11.3 ± 2.6
T_I (s)	0.63 ± 0.08	0.64 ± 0.09	0.62 ± 0.09†
f (breaths/min)	28 ± 7	28 ± 7	29 ± 6
P_{ETCO_2} (mm Hg)	42 ± 6	41 ± 6	42 ± 6
Peak P_{aw} (cm H_2O)	22 ± 9*	23 ± 8*	34 ± 13
PEEP (cm H_2O)	7.7 ± 2.6	7.7 ± 2.9	7.8 ± 3.2
PEEPi (cm H_2O)	2.0 ± 1.4	1.6 ± 1.5	2.6 ± 3.9

*$p < 0.05$, compared to VCV
†Includes an inspiratory flow time of 0.42 ± 0.02 s and a pause time of 0.21 ± 0.06 s.
PRVC = pressure-regulated volume control
PCV = pressure-control ventilation
VCV = volume-control ventilation
WOB = work of breathing
PTP = pressure-time-product
$\dot{W}$ = power output of the inspiratory muscles
$P_{0.1}$ = esophageal pressure in the first 100 ms of inspiration
ΔP_{es} = tidal change in esophageal pressure
V_T = tidal volume
$\dot{V}_I$ = inspiratory flow rate
$\dot{V}_E$ = minute ventilation
T_I = inspiratory time
f = respiratory frequency
P_{ETCO_2} = end-tidal carbon dioxide partial pressure
P_{aw} = airway pressure
PEEP = positive end-expiratory pressure
PEEPi = intrinsic positive end-expiratory pressure

Results

Patient WOB during LPV was markedly elevated, regardless of the ventilator mode. There was a nonsignificant trend toward increased WOB, PTP, and $\dot{W}$ with both PCV and PRVC, compared to VCV (Table 2). Among individual patients, WOB was lowest in 7 patients during VCV, in 5 patients during PCV, in 2 patients during PRVC (Fig. 1). Similarly, PTP was lowest in 7 patients during VCV, in 6 patients during PCV, and in 1 patient during PRVC (Fig. 2).

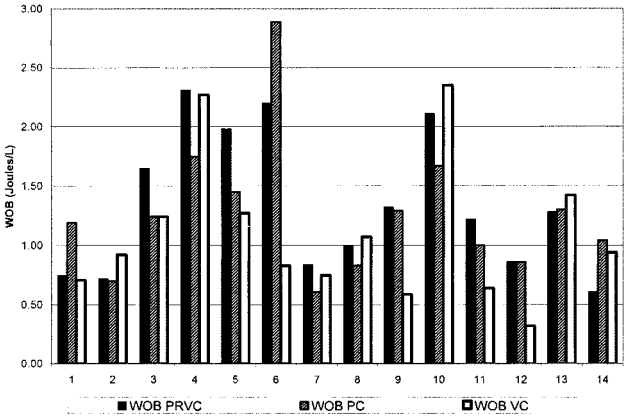

Fig. 1. Patient work of breathing (WOB) in individual patients during volume-control (VC) ventilation, which is denoted by white bars, pressure-control (PC) ventilation, which is denoted by hatched bars, and pressure-regulated volume-control (PRVC) ventilation, which is denoted by solid bars.

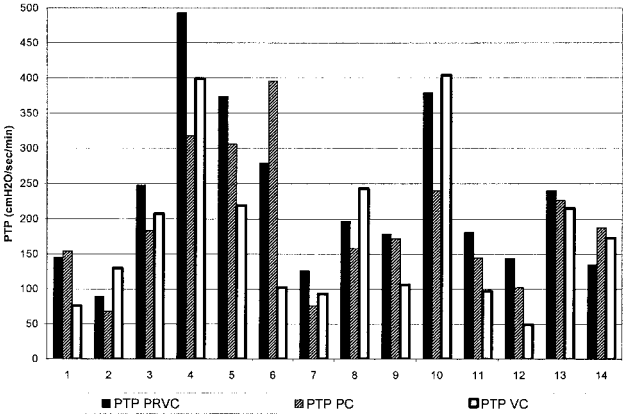

Fig. 2. Pressure-time product (PTP) in individual patients during volume-control (VC) ventilation, which is denoted by white bars, pressure control (PC) ventilation, which is denoted by hatched bars, and pressure-regulated volume-control (PRVC) ventilation, which is denoted by solid bars.

Overall, the inspired V_T was not different between ventilator modes or with the target V_T chosen for each patient (6.4 ± 0.5 mL/kg, $p = 0.13$). Yet in individual patients the inspired V_T markedly exceeded the target V_T (defined as > 0.5 mL/kg):[15] 6 patients during PCV (average: 120 mL, 2.1 mL/kg), 6 patients during PRVC (80 mL, 1.5 mL/kg), and 3 patients during VCV (55 mL, 0.9 mL/kg) (Fig. 3). During VCV, sustained inspiratory effort by 3 patients was sufficient to open the high-pressure servo valve and augment their V_T during the end-inspiratory pause by decreasing the circuit pressure 0.2 cm H_2O below PEEP (Fig. 4) [personal communication, Dräger Medical]. Peak $\dot{V}_I$ and peak P_{aw} were highest during VCV and were significantly different from PRVC. PEEPi, $\dot{V}_E$, total f, $P_{0.1}$, ΔP_{es}, and P_{ETCO_2} were not different between modes.

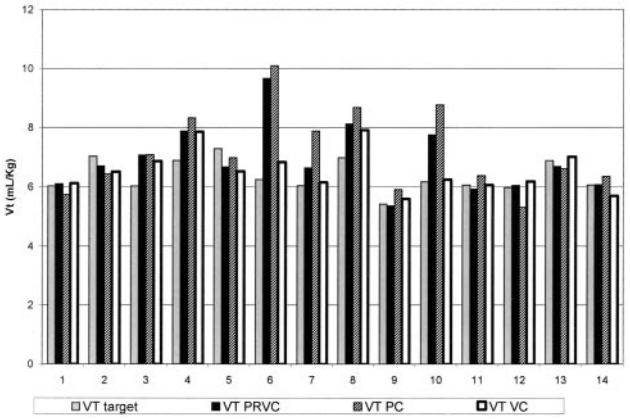

Fig. 3. Comparison of the ventilator-delivered tidal volume (V_T) in individual patients between volume-control (VC) ventilation, which is denoted by white bars, pressure-control (PC) ventilation, which is denoted by hatched bars, pressure-regulated volume-control (PRVC) ventilation, which is denoted by solid bars, and the target V_T, which is denoted by the light solid bars.

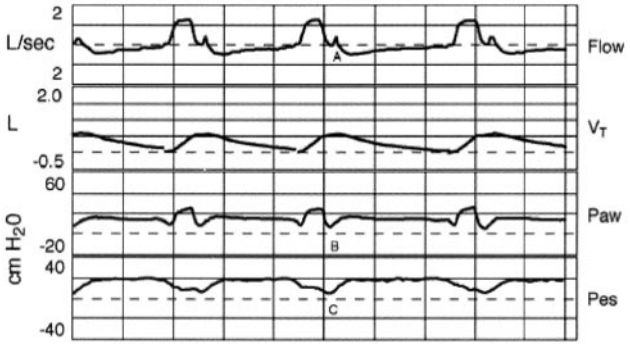

Fig. 4. Scalar waveforms taken from Patient 3 at a pre-set tidal volume (V_T) of 6 mL/kg revealed sustained inspiratory effort with a secondary low-level flow delivery from the ventilator during the end-inspiratory pause (A), resulting in an average ventilator-delivered V_T of 6.9 mL/kg. The Dräger E-2 ventilator has a backup algorithm that controls airway pressure (P_{aw}), even during volume-control ventilation. One of these algorithms allows the high-pressure servo valve to open if the P_{aw} falls -0.2 cm H_2O below baseline [personal communication, Dräger Medical]. A drop in P_{aw} below baseline was evident during the end-inspiratory pause on each breath (B), as was continued patient effort into the inspiratory pause (C). P_{es} = esophageal pressure.

During a brief trial of CPAP, the spontaneous breathing pattern was characterized by an f of 28.4 ± 6.4, an inspired V_T of 279 ± 122 mL (4.6 ± 2.0 mL/kg), a peak $\dot{V}_I$ of 38.4 ± 16 L/min, and a T_I of 0.79 ± 0.19 s. In general, the ventilator-delivered V_T and peak $\dot{V}_I$ during PCV, PRVC, and VCV exceeded what patients could generate during spontaneous breathing, whereas the ventilator T_I was 0.16–0.17 s less than each patient's corresponding T_I during CPAP (Table 3). The ΔV_Tvent-pt was significantly greater during PCV than VCV, whereas the Δ peak $\dot{V}_I$vent-pt was significantly higher during VCV, compared to PCV or

Table 3. Ventilator-to-Patient Differences in Tidal Volume, Peak Inspiratory Flow Rate, and Inspiratory Time Between Modes

	PRVC	PCV	VCV
ΔV_Tvent-pt (mL)	139 ± 91	156 ± 88*	119 ± 102
ΔV_Tvent-pt (mL/kg)	2.3 ± 1.5	2.5 ± 1.3*	1.9 ± 1.6
Δ peak $\dot{V}_I$ vent-pt (L/min)	19 ± 13†	22 ± 16†	38 ± 15
ΔT_I vent-pt (s)	−0.17 ± 0.21	−0.16 ± 0.24	−0.16 ± 0.20

*$p < 0.05$ compared to VCV (Tukey-Kramer post-test)
†$p < 0.001$ compared to VCV (Tukey-Kramer post-test)
PRVC = pressure-regulated volume control
PCV = pressure-control ventilation
VCV = volume-control ventilation
V_T = tidal volume
vent-pt = ventilator-to-patient difference
$\dot{V}_I$ = peak inspiratory flow rate
T_I = inspiratory time

Table 4. Correlation Between Work Measurements in Each Mode and the Calculated Ventilator-to-Patient Difference in Tidal Volume and Peak Inspiratory Flow Rate Delivery

	Pearson Product-Moment Correlation (r)*		
	PRVC	PCV	VCV
ΔV_Tvent-pt vs WOB	−0.45	−0.08	−0.28
ΔV_Tvent-pt vs PTP	−0.37	−0.24	−0.31
Δ peak $\dot{V}_I$vent-pt vs WOB	−0.44	0.03	−0.38
Δ peak V_I vent-pt vs PTP	−0.35	−0.02	−0.37

*$p > 0.05$ for all correlations
PRVC = pressure-regulated volume control
PCV = pressure-control ventilation
VCV = volume control ventilation
V_T = tidal volume
vent-pt = ventilator-to-patient difference
WOB = work of breathing
PTP = pressure-time product
$\dot{V}_I$ = peak inspiratory flow rate

PRVC. However, during VCV and PRVC, both the ΔV_Tvent-pt and the $\Delta \dot{V}_I$vent-pt had only a modest, negative correlation to WOB and PTP, whereas essentially no correlation was found during PCV (Table 4).

Interestingly, in the 4 patients in whom WOB and PTP were highest during VCV, the average ΔV_Tvent-pt was 76 mL (1.4 mL/kg) and the average Δ peak $\dot{V}_I$vent-pt was 41 L/min. In the 5 patients in whom WOB and PTP were highest during PCV (or equaled the values found during PRVC), the ΔV_Tvent-pt was 214 mL (3.6 mL/kg) and the Δ peak $\dot{V}_I$vent-pt was 30 L/min. Likewise, in the 7 patients in whom WOB and PTP were highest during PRVC (or equaled the values found during PCV), the average ΔV_Tvent-pt was 119 mL (1.8 mL/kg), and the Δ peak $\dot{V}_I$vent-pt was 13 L/min.

Discussion

The main findings of this study are as follows. First, regardless of the ventilator mode used to achieve LPV, the average WOB was markedly elevated (> 1 J/L). Second, in sedated patients managed with LPV, PCV and PRVC offered no advantage in reducing WOB, compared to VCV with a high peak $\dot{V}_I$. Third, peak $\dot{V}_I$ during PCV did not achieve the high values previously reported in patients with ALI/ARDS ventilated at a traditional V_T.[7] Fourth, PCV and PRVC often provided a reasonable V_T for LPV, but V_T was not adequately controlled in approximately 40% of patients, despite a reduction in ΔP_{aw} to low levels (10 cm H_2O).

During patient-triggered mechanical ventilation, patient WOB is believed to increase when the ventilator peak $\dot{V}_I$ or the ventilator-delivered V_T is less than the flow or volume demand of the patient.[3–5] In this study, when the modes that caused the highest WOB and PTP were examined in individual patients, the ventilator peak $\dot{V}_I$ and V_T often exceeded what the patient could generate during spontaneous breathing. Furthermore, there was only a modest correlation between either the ΔV_Tvent-pt or the $\Delta \dot{V}_I$vent-pt and WOB and PTP. The lack of a strong relationship between $\dot{V}_I$, V_T, and WOB or PTP may be partially explained by the fact that we used measurements of $\dot{V}_I$ and V_T generated by patients during a brief trial of CPAP as a gross approximation of patient flow and volume demand during mechanical ventilation. This is a precarious assumption, as it is unknown whether the peak $\dot{V}_I$ or V_T generated during CPAP, under high work loads, reflects the peak $\dot{V}_I$ or V_T targeted by patients during mechanical ventilation, when the inspiratory muscles presumably would function under less stress.

Another reason why the ventilator peak $\dot{V}_I$ and V_T did not show a strong correlation to WOB and PTP was the peculiar effects of ventilator-patient asynchrony. Regardless of mode and despite adequate sedation, patients frequently exhibited asynchronous breathing during LPV that limited the effectiveness of traditional ventilator adjustments in peak $\dot{V}_I$ or flow pattern in reducing WOB. Often this occurred in an unusual manner. In several cases, spontaneous breathing during VCV was stimulated by the ventilator, and patient effort commenced only toward the end of the mechanical breath, often negating the beneficial effects of a high $\dot{V}_I$ (Fig. 5). This phenomenon was reported previously by Flick et al,[26] who observed that during controlled ventilation at a low V_T, electromyographic activity and reduced P_{aw} were seen late in inspiration, particularly when the ventilator V_T was close to the patient's spontaneous V_T. This breathing pattern also was documented during the ARDS Network trial, in a patient whose V_T was reduced to 5 mL/kg.[27] In addition, the high mandatory f needed to maintain a baseline $\dot{V}_E$ may have

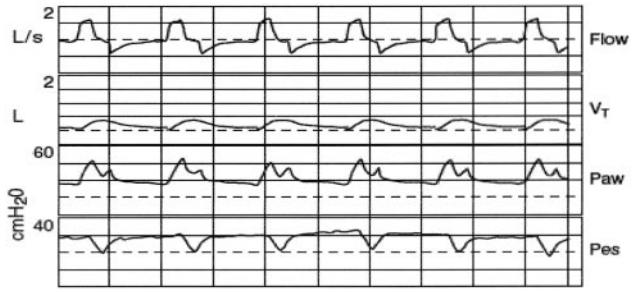

Fig. 5. Scalar waveforms of gas flow, tidal volume (V_T), airway pressure (P_{aw}), and esophageal pressure (P_{es}) taken from Patient 9 during volume-control ventilation. These waveforms reflect a common observation during lung-protective ventilation, whereby a ventilator-triggered breath stimulated the patient's spontaneous breathing effort. The negative deflection in P_{es} consistently occurs at the end of the mechanical breath, so that the beneficial effects of a high ventilator inspiratory flow rate are negated.

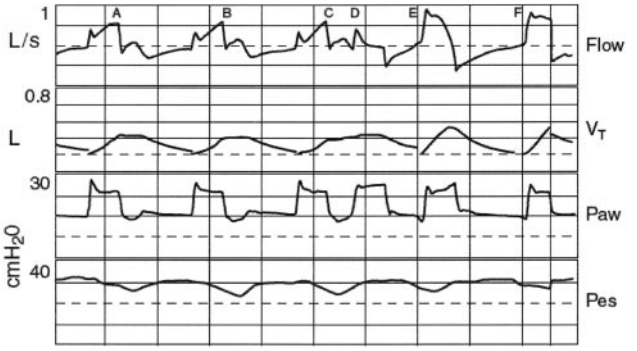

Fig. 6. Scalar waveforms of gas flow, tidal volume (V_T), airway pressure (P_{aw}), and esophageal pressure (P_{es}) taken from Patient 13 during pressure-control ventilation. This figure represents a common finding whereby chest-wall stiffening at the onset of a mechanical breath results in an initially low ventilator flow delivery that begins to taper off. When the patient's inspiratory effort begins later in the inspiratory phase, the resulting ventilator flow paradoxically becomes ascending, and inspiratory effort continues into the expiratory phase (breaths A and B). The same phenomenon occurs during breath C, which results in a double-triggered breath (D). Breaths E and F represent conventional patient-triggered breaths whereby the ventilator flow pattern changes according to the intensity of inspiratory effort.

contributed to this particular type of asynchrony. In our experience, lowering the mandatory f results in better synchrony in some patients, while in others it appears to have no effect.

Furthermore, during VCV, inspiratory effort sometimes continued during the end-inspiratory pause and likely contributed to the elevated WOB. In the Dräger ventilators, T_I is set directly, while the portion dedicated to inspiratory flow is determined by the V_T and the peak $\dot{V}_I$, so that any remaining T_I after V_T delivery is converted into an end-inspiratory pause. Acute alveolar edema was reported[4] during LPV with a Dräger Evita 1 ventilator, when inspiratory efforts were sustained into the end-inspiratory pause. Unlike the Dura E-2 ventilator, the high-pressure servo valve of the Evita 1 did not open when the circuit pressure fell below the PEEP level, so that the imposed WOB was extraordinarily high.[4] This situation presents something of a clinical quandary during LPV with VCV. If a high peak $\dot{V}_I$ is used to alleviate increased WOB, the resulting brief T_I (coupled with sustained inspiratory effort) may result in double-triggered breaths and a loss of lung-protection.[5] Contrarily, increasing T_I by using an end-inspiratory pause, a lower peak $\dot{V}_I$, or a decreasing-ramp flow pattern may result in elevated WOB but likely would keep V_T closer to the LPV target.[4,5]

Of particular interest were the effects of asynchrony during PCV and PRVC. We noted that when patients stiffened their chest wall at the beginning of a time-triggered mechanical breath, the ventilator flow rapidly tapered off. Within the same breath, patients subsequently made inspiratory efforts that paradoxically caused the flow pattern to transform from a descending ramp into an ascending ramp, thus negating the beneficial effects of a decreasing-ramp flow pattern on WOB (Fig. 6). During PRVC we noted that when a patient's effort resulted in a delivered V_T above the pre-set target, typically there was a progressive decrease in peak P_{aw} and peak $\dot{V}_I$ over several breaths, with a corresponding increase in ΔP_{es} and WOB. This reflected the ventilator's attempt to reduce V_T toward the target while a greater proportion of the inspiratory work load was shifted onto the patient. Furthermore, we observed situations in which a patient exhibiting an asynchronous pattern would stiffen his/her chest wall on one breath, causing a decrease in V_T, and then make a vigorous inspiratory effort on the subsequent breath, resulting in a large increase in V_T. Because P_{aw} is automatically titrated during PRVC to control V_T, asynchrony often resulted in the V_T, peak $\dot{V}_I$, and flow pattern being in constant flux (Fig. 7).

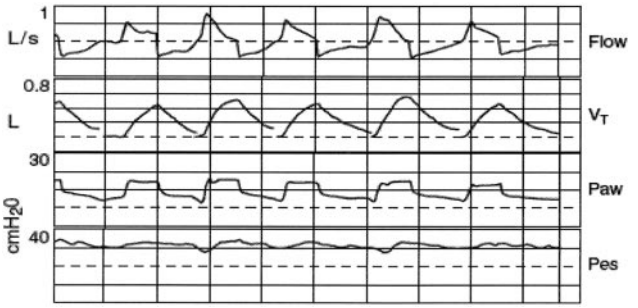

Fig. 7. Scalar waveforms of gas flow, tidal volume (V_T), airway pressure (P_{aw}), and esophageal pressure (P_{es}) taken from Patient 4 during pressure-regulated volume-control ventilation. The peak flow, flow pattern, V_T, and peak P_{aw} changes with each breath as the ventilator attempts to regulate V_T while the flow pattern varies with changes in patient effort.

In this study the lower peak $\dot{V}_I$ found in PCV was caused by the need to reduce the inspiratory pressure level to constrain V_T. This was accomplished during PRVC by the ventilator's automated control of peak P_{aw} to maintain the V_T target. These results are contrary to our previous study, in which WOB was significantly lower during PCV, compared to VCV.[7] In that study the target V_T was 10 ± 2.5 mL/kg, so that a higher peak P_{aw} (33 ± 6 cm H_2O) was required during PCV that resulted in a higher peak $\dot{V}_I$ (103 ± 23 L/min), compared to the current study (23 ± 8 cm H_2O and 61 ± 16 L/min). Therefore, assumptions regarding the efficacy of pressure-regulated modes to reduce patient WOB based upon traditional V_T ventilation may not apply when these modes are used for LPV.

Another finding of this study is that patient-triggered, pressure-regulated ventilation frequently resulted in less precise control of V_T, along with substantial negative swings in intrathoracic pressure. Ventilator-associated lung injury is caused by a high V_T that coincides with a large change in *transpulmonary* pressure. Animal studies have shown that lung injury can be induced by high-volume negative-pressure ventilation.[28,29] Recommendations for LPV include the provision that tidal pressure changes should be ≤ 20 cm H_2O.[30] In theory, pressure-regulated modes can be used for LPV by adjusting the ΔP_{aw} to ≤ 20 cm H_2O to produce a V_T of 6 mL/kg. However, during patient-triggered, pressure-regulated ventilation the clinician must consider what happens to transpulmonary pressure. If the V_T *substantially* exceeds 6 mL/kg, then transpulmonary pressure also is increased and may exceed the recommended limits for LPV. We found the average ΔP_{es}, a surrogate for tidal pleural pressure change, was approximately 15–17 cm H_2O, while P_{aw} was regulated to levels > 20 cm H_2O. The substantial loss of V_T control that occurred in some patients suggests that occult high-pressure, high-V_T ventilation may persist during pressure-regulated LPV, despite an appropriately set ΔP_{aw}. It is interesting to note that when pressure-regulated modes were used in previous clinical trials of LPV,[31–33] great care was taken to ensure that V_T did not exceed 6 mL/kg, by liberal use of sedation and, in some instances, the addition of small doses of neuromuscular blocking agents to weaken patient's inspiratory efforts.[33]

A limitation of this study is that only one type of ventilator was used, and any generalization of our results is restricted by how ventilators differ in mode design. For example, in the Dräger Dura E-2 version of PRVC (Auto-Flow), P_{aw} is titrated in increments of 1–3 cm H_2O per breath to achieve the V_T target. Auto-Flow also incorporates the "free breathing" feature used in airway-pressure-release ventilation, so that patients can actively inspire or expire at any point during the inspiratory cycle. Other versions of PRVC that use different inspiratory pressure titration algorithms or do not incorporate the "free-breathing" feature will respond somewhat differently than the Dräger E-2 ventilator during patient-triggered breaths. Therefore, caution should be used in generalizing our results to PRVC in other ventilators.

In addition, the study time periods used in our protocol may have been too brief for complete adaptation, and thus may not reflect how each mode affects WOB over time. To our knowledge, there are no studies describing the time course for how mechanically ventilated patients adapt their breathing pattern to sudden changes in inspiratory work load. In laboratory experiments, normal subjects begin to adapt to a sudden change in work load within one breath, and the adaptation is progressive.[34,35] However, the breathing pattern typically returns to either baseline or a new equilibrium within 3–6 breaths.[34,36,37] Therefore, the available data suggest that allowing 10 min for adaptation to each breathing mode is reasonable. Our interest was to make a preliminary assessment of WOB and V_T control during LPV, comparing the various modes used to manage patients with ALI/ARDS. Therefore, we were concerned that extending observations over a longer time period would increase the likelihood that later-occurring changes in WOB could be caused by changes in the patient's condition (such as a sudden increase in pain or fever), rather than associated with the mode of ventilation.

Conclusions

During LPV in patients sedated to a Ramsey score of approximately 4, patient WOB was markedly elevated, regardless of ventilator mode. In addition, we found that PCV and PRVC provided no advantage in reducing WOB, compared to VCV with a high peak $\dot{V}_I$. We attributed this to the reduction in P_{aw} necessary to constrain V_T delivery within the LPV range, and in consequence resulted in a substantially reduced peak $\dot{V}_I$. Inadequate control of V_T coupled with substantial negative swings in pleural pressure may result in occult high-volume, high-pressure ventilation during PCV and PRVC, despite a relatively low P_{aw}. Therefore, clinicians should be particularly vigilant in monitoring V_T stability when using PCV and PRVC for patient-triggered LPV.

REFERENCES

1. Tuxen DV. Permissive hypercapnia. In: Tobin MJ, editor. Principles and practice of mechanical ventilation. New York: McGraw Hill; 1994:371–392.
2. Tuxen DV. Permissive hypercapnic ventilation. Am J Respir Crit Care Med 1994;150(3):870–874.
3. Marini JJ, Rodriguez RM, Lamb V. The inspiratory workload of patient-initiated mechanical ventilation. Am Rev Respir Dis 1986; 134(5):902–909.
4. Kallet RH, Alonso JA, Luce JM, Matthay MA. Exacerbation of acute pulmonary edema during assisted mechanical ventilation using a

low-tidal volume, lung-protective ventilator strategy. Chest 1999; 116(6):1826–1832.
5. Kallet RH, Alonso JA, Diaz M, Campbell AR, Mackersie RC, Katz JA. The effects of tidal volume demand on work of breathing during simulated lung protective ventilation. Respir Care 2002;47(8):898–909.
6. Berger AJ, Mitchell RA, Severinghaus JW. Regulation of respiration. Part 1. N Engl J Med 1977;297(2):92–97.
7. Kallet RH, Campbell AR, Alonso JA, Morabito DJ, Mackersie RC. The effects of pressure control versus volume control assisted ventilation on patient work of breathing in acute lung injury and the acute respiratory distress syndrome. Respir Care 2000;45(9):1085–1096.
8. Riverso P, Bernardi PL, Corsa D, Morra MG, Paganini G, Parigi F. [A comparison of ventilation techniques in ARDS. Volume controlled vs pressure regulated volume control.] Minerva Anestesiol 1998;64(7–8):339–343. (Article in Italian)
9. Amato MB, Barbas CS, Bonassa J, Saldiva PH, Zin WA, Carvalho CR. Volume-assured pressure support ventilation (VAPSV): a new approach for reducing muscle workload during acute respiratory failure. Chest 1992;102(4):1225–1234.
10. Alonso JA, Kallet RH, Siobal M, Kraemer R, Marks JD. Does autoflow optimize inspiratory flow? A lung model study [abstract]. Crit Care Med 1999;27(Suppl 1):A93.
11. Cinnella G, Conti G, Lofaso F, Lorino H, Harf A, Lemaire F, Brochard L. Effects of assisted ventilation on the work of breathing: volume-controlled versus pressure-controlled ventilation. Am J Respir Crit Care Med 1996;153(3):1025–1033.
12. Haas CF, Branson RD, Folk LM, Campbell RS, Wise CR, Davis K, et al. Patient-determined inspiratory flow during assisted mechanical ventilation. Respir Care 1995;40(7):716–721.
13. MacIntyre NR, McConnell R, Cheng KC, Sane A. Patient-ventilator flow dyssynchrony: flow-limited versus pressure-limited breaths. Crit Care Med 1997;25(10):1671–1677.
14. Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, et al. The American European consensus conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med 1994;149(3 Pt 1):818–824.
15. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. N Engl J Med 2000;342(18):1301–1308.
16. Baydur A, Behrakis PK, Zin WA, Jaeger M, Milic-Emili J. A simple method for assessing the validity of the esophageal balloon technique. Am Rev Respir Dis 1982;126(5):788–791.
17. Marini JJ, Smith TC, Lamb V. Estimation of inspiratory muscle strength in mechanically ventilated patients: the measurement of maximal inspiratory pressure. J Crit Care 1986;1(1):32–38.
18. de Durante G, del Turco M, Rustichini L, Cosimini P, Giunta F, Hudson LD, et al. ARDSNet lower tidal volume ventilatory strategy may generate intrinsic positive end-expiratory pressure in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 2002;165(9):1271–1274.
19. Bonmarchand G, Chevron V, Menard JF, Girault C, Moritz-Berthelot F, Pasquis P, Leroy J. Effects of pressure ramp slope values on the work of breathing during pressure support ventilation in restrictive patients. Crit Care Med 1999;27(4):715–722. *Erratum in: Crit Care Med 1999;27(7):1404.*
20. Ramsay MAE, Savege TM, Simpson BRJ, Goodwin R. Controlled sedation with alphaxalone-alphadolone. Br Med J 1974;2(920):656–659.
21. Blanch PB, Banner MJ. A new respiratory monitor that enables accurate measurements of work of breathing: a validation study. Respir Care 1994;39(9):897–905.
22. Petros AJ, Lamond CT, Bennett D. The Bicore pulmonary monitor. Anaesthesia 1993;48(11):985–988.
23. Sassoon CS, Light RW, Lodia R, Sieck GC, Mahutte CK. Pressure-time product during continuous positive airway pressure, pressure support ventilation, and T-piece during weaning from mechanical ventilation. Am Rev Respir Dis 1991;143(3):469–475.
24. Murray JF, Matthay MA, Luce JM, Flick MR. An expanded definition of the adult respiratory distress syndrome. Am Rev Respir Dis 1988;138(3):720–723.
25. Glantz SA. Primer of biostatistics. New York: McGraw-Hill; 1997: 92–96.
26. Flick GR, Bellamy PE, Simmons DH. Diaphragmatic contraction during assisted mechanical ventilation. Chest 1989;96(1):130–135.
27. Kallet RH, Luce JM. Detection of patient-ventilator asynchrony during low tidal volume ventilation, using ventilator waveform graphics. Respir Care 2002;47(2):183–185.
28. Mascheroni D, Kolobow T, Fumagalli R, Moretti MP, Chen V, Buckhold D. Acute respiratory failure following pharmacologically induced hyperventilation: an experimental animal study. Intensive Care Med 1988;15(1):8–14.
29. Dreyfuss D, Soler P, Basset G, Saumon G. High inflation pressure pulmonary edema: respective effects of high airway pressure, high tidal volume, and positive end-expiratory pressure. Am Rev Respir Dis 1988;137(5):1159–1164.
30. Lachmann B. Open up the lung and keep the lung open. Intensive Care Med 1992;18(6):319–321.
31. Hickling KG, Walsh J, Henderson S, Jackson R. Low mortality rate in adult respiratory distress syndrome using low volume, pressure-limited ventilation with permissive hypercapnia: a prospective study. Crit Care Med 1994;22(10):1568–1578.
32. Amato MB, Barbas CS, Medeiros DM, Magaldi RB, Schettino GP, Lorenzi-Filho G, et al. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. N Engl J Med 1998;338(6):347–354.
33. Amato MB, Barbas CS, Medeiros DM, Schettino Gde P, Lorenzi Filho G, Kairalla RA, et al. Beneficial effects of the "open lung approach" with low distending pressures in acute respiratory distress syndrome: a prospective randomized study on mechanical ventilation. Am J Respir Crit Care Med 1995;152(6 Pt 1):1835–1846.
34. Campbell EJ, Dinnick OP, Howell JB. The immediate effects of elastic loads on the breathing of man. J Physiol 1961;156:260–273.
35. Altose MD, Kelsen SG, Cherniack. Respiratory responses to changes in airflow resistance in conscious man. Respir Physiol 1979;36(2): 249–260.
36. Freeman S, Weinstein SA. Effects of external elastic and threshold loading on breathing in man. J Appl Physiol 1965;20(3):469–472.
37. Pope H, Holloway R, Campbell EJ. The effects of elastic and resistive loading of inspiration on the breathing of conscious man. Respir Physiol 1968;4(3):363–372.