

Biologic Variability in Mechanical Ventilation Rate and Tidal Volume Does Not Improve Oxygenation or Lung Mechanics in Canine Oleic Acid Lung Injury

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Mechanical ventilation in patients with acute respiratory distress syndrome and acute lung injury (ALI) remains a difficult challenge because of the conflict between maintaining adequate gas exchange and furthering lung injury via overdistention. In a recent study, Lefevre and colleagues (*Am. J. Respir. Crit. Care Med.* 1996;154:1567-1572) suggested that mechanical ventilation with natural biologic variability (BV) in breath-to-breath respiratory frequency (f) and V_T could reduce lung injury and improve gas exchange without increases in mean airway pressure (P_{aw}) or peak inspiratory pressure (PIP). However, significant differences in cardiac output (CO), P_{aCO_2} , pH, and delivered V_T between the treatment groups in their study could have influenced these results. Because of the potential implications of these findings for patient care, we attempted to confirm these findings by Lefevre and colleagues in a canine model of oleic acid-induced lung injury. Eighteen mongrel dogs were anesthetized in the supine position, paralyzed, and mechanically ventilated with 50% O_2 at $f = 15$ breaths/min, and V_T was adjusted to achieve an end-tidal CO_2 of 30 to 35 mm Hg. Lung injury was produced by infusion of 0.06 ml/kg oleic acid solution into the right atrium over a 30-min period. Animals were then randomized to either conventional ventilation at the baseline settings ($n = 9$) or to BV at the same mean V_T and f ($n = 9$). Both groups received comparable degrees of injury, and hemodynamic and ventilatory parameters were closely matched, with no differences in mean V_T , PIP, mean P_{aw} , P_{aCO_2} , pH, CO, pulmonary artery occlusion pressure, or arterial pressure (Pa). However, no differences between the two groups were found in P_{aO_2} , shunt, or static compliance over a 4-h period. When hemodynamic and ventilatory parameters were well matched in a canine model of ALI, BV showed no advantage over conventional ventilation at constant V_T and f .

In the lungs of patients with acute respiratory distress syndrome (ARDS), a large portion of alveoli are atelectatic or fluid-filled (1), whereas other lung regions are aerated and relatively unaffected by the disease process (2). Traditional techniques of mechanical ventilatory assistance involve a generous tidal volume (V_T) and positive end-expiratory pressure (PEEP). However, many animal studies suggest that this approach can perpetuate or exacerbate lung injury from high pressures and overdistention of the aerated lung regions. Consequently, there has been considerable interest in alternative ventilatory methods to improve oxygenation in these critically ill patients.

In a pig oleic acid (OA) model of ARDS, a novel mechanical ventilatory approach utilized a computer programmed to vary the breath-to-breath respiratory frequency (f) and V_T

with natural biologic variability (3). Compared with conventional mechanical ventilation (CV) at the same mean f and V_T , such biologically variable ventilation (BV) was associated with a higher P_{aO_2} and static compliance (Cst), and with reduced shunt and lung water content over a 4-h observation period. These salutary changes could be explained by recruitment of small airways and alveoli, which the investigators who conducted the study attributed to an intrinsic characteristic of the biologic variability in f and V_T . For example, increased recruitment could have been induced with the larger BV breaths, but in some way that was different than that with regularly spaced large tidal volumes (sighs), which have had inconsistent effects on arterial oxygenation in previous studies (4-6). Decreased lung water in the BV group was interpreted to represent decreased ventilation-associated lung injury, which could also be explained by better airways recruitment.

The results of this initial experience with BV are potentially important because improvements in oxygenation appear to have been achieved without increased risk of volutrauma to the lungs. If validated, this novel strategy could represent a significant advance in patient management. However, there were significant differences in cardiac output (CO), P_{aCO_2} , pH, and actual delivered V_T between the CV and BV groups, which could have influenced the results of the study. Because of the potential implications of these findings for patient care, we have attempted to confirm these results in a dog OA model of ARDS. In contrast to the results of Lefevre and colleagues, we found no improvement in P_{aO_2} , Cst or shunt with BV in our experiments.

METHODS

Experimental Preparation

The study was approved by the Animal Care and Use Committee of The Johns Hopkins University. Eighteen mongrel dogs weighing 9 to 31 kg (mean: 15.9 kg) were anesthetized with pentobarbital sodium (30 mg/kg intravenously), orally intubated, and placed in the supine position. Pancuronium (3 mg bolus, followed by 1 to 1.5 mg/h intravenously) was administered for muscle relaxation. Isoflurane was administered at 1 to 1.5% end-tidal in 50% O_2 for maintenance of anesthesia. A catheter was placed in the femoral artery for blood gas sampling and monitoring of arterial pressure (Pa). A size 7.5-French Edwards Swan-Ganz catheter was inserted into the pulmonary artery via the external jugular vein. Mixed venous blood was sampled from the distal end of the pulmonary artery catheter. An esophageal balloon was inserted into the esophagus, and located at the point of maximum swings in tidal pressure, and its pressure (Peso) was continuously recorded. All pressure transducers were zero-referenced to the midchest level. Lactated Ringer's solution was given as a bolus until the animal's initial pulmonary artery occlusion pressure (Ppao) was 8 mm Hg, and was then infused continuously at 10 ml/kg/h for the duration of the experiment. At the end of the experiment the animal was killed by intravenous injection of saturated potassium chloride, after supplementation of anesthesia with additional barbiturate.

Mechanical ventilation was provided via a portable piston ventilator (PLV-102; Lifecare, Lafayette, CO), which was modified by the

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manufacturer to allow remote computer control. The ventilator was set at 15 breaths/min, with the V_T adjusted to maintain the end-tidal P_{CO_2} (P_{ETCO_2}) at 30 to 35 mm Hg. Two sighs (each equal to three tidal breaths) were induced in each animal by occluding the expiratory limb of the ventilatory circuit before beginning control measurements. Compliance of the ventilator circuit was 0.57 ml/cm H_2O .

After administration of the initial fluid bolus was completed, baseline measurements were obtained of hemodynamic, respiratory, and lung mechanics parameters. These included heart rate, Pa, right atrial pressure (Pra), pulmonary artery pressure (Ppa), and Ppao. All were recorded on a Gould 2600S oscillograph (Gould, Inc., Cleveland, OH). CO was measured by thermodilution, using a 5 ml injection of saline at room temperature (mean of three measurements). Measurements of arterial and mixed venous blood gases (Model 248 pH/Blood Gas Analyzer; Ciba Corning Diagnostics, Medfield, MA) and hemoglobin concentrations (OSM3 Hemoximeter; Radiometer, Copenhagen, Denmark) were also made. The O_2 saturations of arterial and mixed venous blood gas samples were calculated with the equations for the pH-corrected O_2 dissociation curve (7). Pulmonary vascular resistance (Rpv) and shunt fraction (venous admixture, Q_s/Q_T) were calculated with standard formulas (8). Static compliance was obtained by clamping the expiratory limb of the ventilatory circuit at end-inspiration for 1 to 2 s to obtain a plateau pressure. The V_T used for calculation of compliance was that set on the ventilator. FRC, measured in triplicate with the helium dilution method, and a quasistatic pressure-volume (PV) curve (three cycles at 2 L/min at a P_{aw} between 2 and 30 cm H_2O) were obtained at baseline and after OA injury. For the last five animals in the CV group and last six animals in the BV group, in-

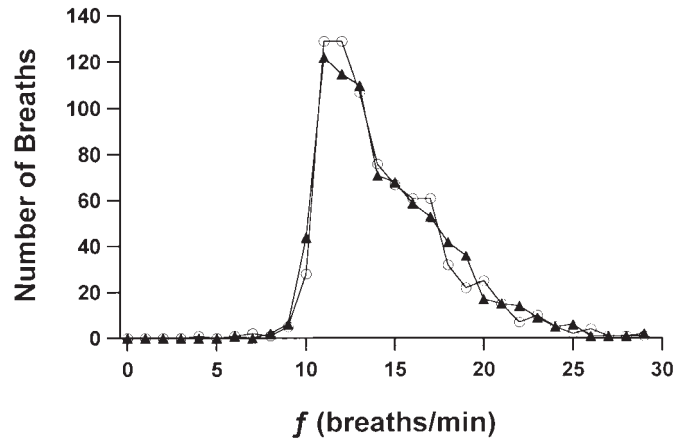


Figure 2. Histograms of BV f file before (open symbols) and after (closed symbols) editing. Editing maintained the overall shape of the distribution. Both distributions have a mean f of 15 breaths/min.

spiratory flow was measured with a pneumotachograph (Hans Rudolph Inc., Kansas City, MO), and instantaneous flow and airway pressures (P_{aw} and P_{eso}) were digitized at 10 Hz and stored in a computer (Macintosh PM7100/80; Apple Computer, Cupertino, CA) using a Superscope data-acquisition system (GW Instruments, Inc., Somerville, MA). These acquired data were used for the breath-by-breath analysis of mean P_{aw} , peak inspiratory pressure (PIP), and delivered V_T , as subsequently described.

Lung Injury

Lung injury was induced by infusion of 0.06 ml/kg pure OA (Sigma Chemical Co., St. Louis, MO), diluted 1:2 with absolute ethanol, over a period of 30 min, into the right atrial port of the Swan-Ganz catheter with the animal in the supine position. This dose was chosen on the basis of preliminary experiments designed to identify the OA dose necessary to achieve a level of lung injury similar to that in the recently reported study of BV in pigs (3). At the end of OA infusion, animals were randomly assigned to one of two ventilatory modes: CV, fixed at the baseline V_T and f of 15 breaths/min, or BV, with the same mean f and V_T as subsequently described. As in the previous study of BV (3), no PEEP was used in either group. Ventilation was continued with either CV or BV for the duration of the experiment, and hemodynamic, respiratory, and lung mechanics data were obtained every 30 min for 4 h. Four animals in the CV group and three animals in the BV group did not survive to 4 h, but all animals lasted at least through the 180-min measurement period.

BV Ventilation System

The Superscope data-acquisition system used to digitize the P_{aw} , P_{eso} , and flow signals also directed the PLV-102 ventilator to deliver biologic variations in f and V_T according to a previously generated file of interbreath periods from an awake, spontaneously breathing, quiescent dog (provided by Dr. Paul Murray and Jim Palazzo of the Department of Anesthesia, Cleveland Clinic). The original breathing file con-

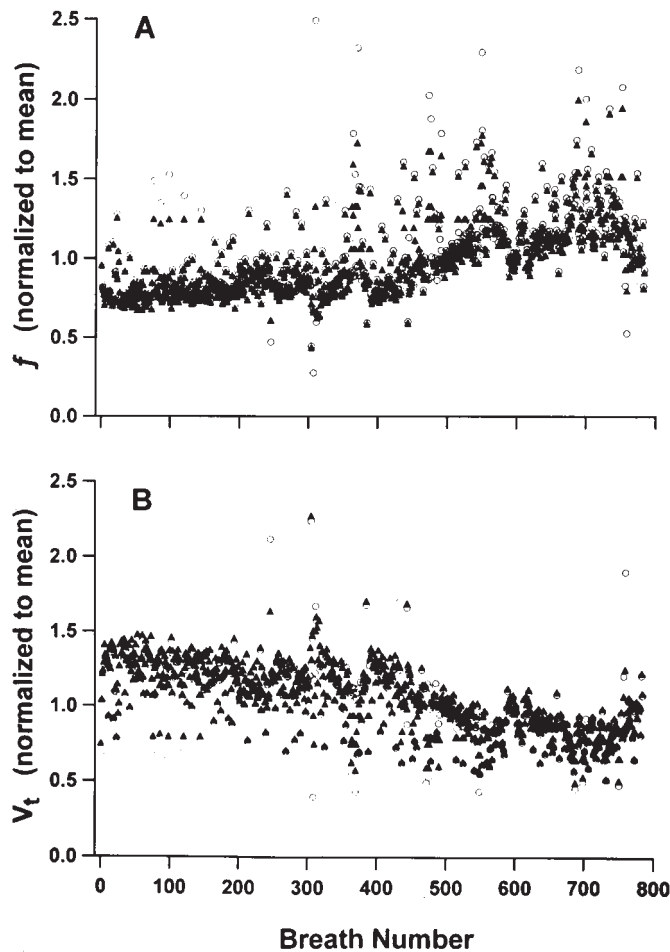


Figure 1. (A) BV f file and (B) corresponding V_T file before (open symbols) and after (closed symbols) editing, plotted against breath number. Breaths with too high or too low frequencies were adjusted to meet mechanical constraints of the BV ventilator system.

TABLE 1
CHARACTERISTICS OF THE BV f AND V_T FILES

	f (breaths/min)	Normalized V_T
Mean	15	1
SD	3.6	0.23
10th percentile	11.3	0.75
25th percentile	12.2	0.88
50th percentile	14.2	1.06
75th percentile	17.1	1.23
90th percentile	19.9	1.33

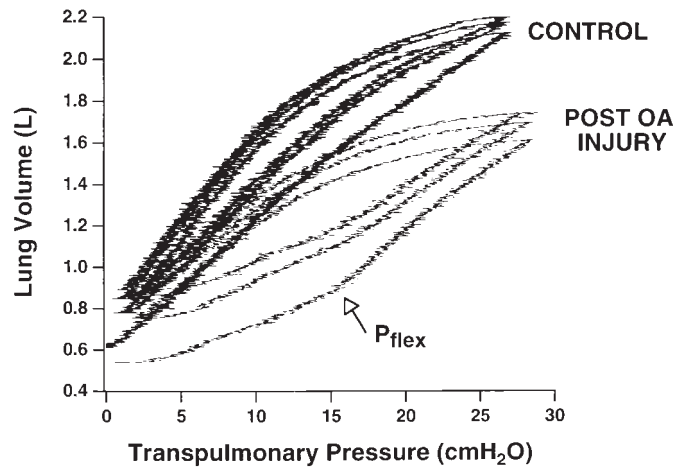


Figure 3. PV curves before (darker line) and 240 min after (lighter line) OA-induced lung injury. PV curves were acquired from Paw values of 2 to 30 cm H₂O for three cycles each, at a constant air flow of 2 L/min. Upward shift with subsequent cycles reflects lung volume recruitment. The noisy appearance of the curves is caused by cardiac oscillations in Peso. Note P_{flex} on the inspiratory limb of the PV curve of the OA-injured lung.

tained 784 breaths with an *f* value of 37 ± 9.7 breaths/min (mean \pm SD) (coefficient of variation [CV]: 26.2%). This data set was scaled to a mean *f* of 15 breaths/min for use in this protocol. It was necessary to edit the file such that the *f* and V_T differences between any two adjacent breaths were within limits imposed by the mechanical capability of the ventilator. This resulted in minor changes in the frequency spectrum (Figures 1 and 2). The edited and scaled file contained 784 breaths with an *f* of 15 ± 3.6 breaths/min (CV: 24%). The minimum and maximum *f* of the file were 6.5 and 30 breaths/min, respectively (Figure 1A). Histograms of the *f* distribution before and after editing are shown in Figure 2. A corresponding V_T file was generated from this *f* file on the basis of the control V_T for a given animal: the V_T of each breath was calculated such that minute ventilation ($\dot{V}_E = f \times V_T$) remained constant (Figure 1B). The mean *f* and V_T of these files were thus equal to the *f* and V_T of the baseline ventilation settings. Because

inspiratory flow and the I:E ratio were kept constant, larger breaths had longer inspiratory times followed by longer expiratory times. Table 1 presents the characteristics of scaled *f* and normalized V_T files after editing. For example, 50% of breaths (25th to 75th percentile) were within the *f* range of 12.2 to 17.1 breaths/min with V_T between 88% and 123% of the control value. At a mean *f* of 15 breaths/min, the BV file lasted about 52 min, and thus was repeated several times during the 4-h experiments. Ventilator settings were transiently returned to the baseline settings for 3 to 5 min while hemodynamic and compliance measurements were made, after which BV was resumed.

PV curves were obtained before and after OA-induced lung injury, with examples shown in Figure 3. A computer-controlled system measured quasistatic PV curves during inflation and deflation of the lungs at a constant flow of 2 L/min from values of Paw of 2 to 30 cm H₂O for three cycles. Paw, Peso, and airway opening flow signals were digitized and stored on the computer for subsequent analysis. The PV curve of the OA-injured lung often exhibits a change in slope (P_{flex}) on the early-portion of its inspiratory limb, as has been described in many patients with ARDS (9–11). P_{flex} was determined from the PV curves as the intersection of the linear projections of the early and midportions of the first cycle inspiratory curve.

Statistical Analysis

Data were subjected to longitudinal analysis, using the STATA statistical software package (Stata Co., College Station, TX). This analysis takes into account the missing data for animals that did not survive for the full 4 h of the experimental period, and fits linear models to compare the time courses of different parameters, with the assumption that data values depend upon each other over time. The data values at the time of development of initial injury were used as the “baseline” values for the longitudinal analysis. Student’s *t* test was used for single-time-point comparisons between groups. Survival differences between groups were tested with a log-rank test (Stata). A value of *p* < 0.05 was considered significant in both longitudinal analysis and with Student’s *t* test. Data are presented as mean \pm SEM unless otherwise noted.

RESULTS

OA infusion caused significant lung injury, with decreased Pa_{O₂} and Cst and increased airway pressures observed at 30 min after OA infusion in both the CV and BV groups. Comparable levels of injury were achieved in the two groups, with

TABLE 2
HEMODYNAMIC DATA*

Parameter	Baseline	30 min	60 min	90 min	120 min	150 min	180 min	210 min	240 min
Pa, mm Hg									
CV	95 \pm 4	88 \pm 4	101 \pm 6	99 \pm 4	99 \pm 6	97 \pm 8	100 \pm 9	102 \pm 15 [§]	102 \pm 14 [‡]
BV	102 \pm 8	94 \pm 6	102 \pm 6	103 \pm 6	104 \pm 6	102 \pm 7	104 \pm 7	99 \pm 7 [¶]	100 \pm 7 [§]
Ppa, mm Hg									
CV	18 \pm 1 [†]	20 \pm 2	21 \pm 2	23 \pm 2	26 \pm 3	27 \pm 3	29 \pm 3	30 \pm 4 [§]	37 \pm 4 ^{††}
BV	15 \pm 1	17 \pm 1	18 \pm 1	19 \pm 2	20 \pm 2	23 \pm 3	26 \pm 3	23 \pm 2 [¶]	24 \pm 2 [§]
Ppao, mm Hg									
CV [‡]	8.3 \pm 0.5	8.0 \pm 1.1	9.4 \pm 1.3	9.1 \pm 1.3	9.4 \pm 1.2	8.8 \pm 1.5	9.6 \pm 1.4	8.7 \pm 1.5 [§]	8.8 \pm 1.3 [‡]
BV	6.4 \pm 0.9	6.3 \pm 1.0	6.4 \pm 1.1	6.8 \pm 1.1	7.3 \pm 1.3	7.4 \pm 1.3	7.4 \pm 1.1	7.0 \pm 1.4 [§]	6.5 \pm 1.5 [‡]
Rpv, mm Hg/min/L									
CV [‡]	3.2 \pm 0.5	6.7 \pm 1.2	6.5 \pm 1.6	8.8 \pm 2.7	10.8 \pm 3.3	12.1 \pm 3.8	13.6 \pm 4.3	14.0 \pm 5.7 [§]	15.9 \pm 5.6 [‡]
BV	2.9 \pm 0.5	4.1 \pm 0.5	4.4 \pm 0.6	5.2 \pm 0.7	6.0 \pm 0.8	8.2 \pm 1.3	8.2 \pm 0.9	8.2 \pm 1.3 [‡]	8.4 \pm 1.4 [§]
CO, L/min/kg									
CV	0.24 \pm 0.04	0.14 \pm 0.01	0.14 \pm 0.02	0.14 \pm 0.02	0.13 \pm 0.02	0.14 \pm 0.02	0.15 \pm 0.03	0.14 \pm 0.02 [§]	0.15 \pm 0.02 [‡]
BV	0.2 \pm 0.02	0.16 \pm 0.02	0.17 \pm 0.02	0.15 \pm 0.02	0.13 \pm 0.02	0.11 \pm 0.00	0.13 \pm 0.01	0.12 \pm 0.01 [¶]	0.12 \pm 0.01 [¶]
Hb, g%									
CV	9.6 \pm 0.8	10.5 \pm 0.8	10.9 \pm 0.7	11.2 \pm 0.6	11.6 \pm 0.6	12.1 \pm 0.7	12.7 \pm 0.8	12.2 \pm 1.1 [§]	12.2 \pm 1.6 [‡]
BV	9.3 \pm 0.8	11.4 \pm 0.7	11.4 \pm 0.8	11.1 \pm 1.0	11.9 \pm 1.0	12.1 \pm 1.2	12.6 \pm 1.1	11.6 \pm 1.0 [¶]	11.8 \pm 1.0 [¶]

Definition of abbreviations: CO = cardiac output; Hb = hemoglobin; Pa = arterial pressure; Ppa = pulmonary artery pressure; Ppao = pulmonary artery occlusion pressure; Rpv = pulmonary vascular resistance.
 * Values are mean \pm SEM. Times are times after OA injury. n = 9 except [‡]n = 4, [†]n = 5, [§]n = 6, [¶]n = 7, ^{||}n = 8.
[†] *p* < 0.05 for differences between groups.

TABLE 3
RESPIRATORY GAS DATA*

Parameter	Baseline	30 min	60 min	90 min	120 min	150 min	180 min	210 min	240 min
Pa _{O₂} , mm Hg									
CV	289 ± 19	89 ± 10	85 ± 10	86 ± 14	83 ± 16	69 ± 10	62 ± 10	71 ± 11 [†]	53 ± 10 [†]
BV	264 ± 8	77 ± 6	66 ± 4	75 ± 8	78 ± 11	81 ± 16	82 ± 20	94 ± 24 ^{††}	95 ± 28 ^{††}
Pa _{CO₂} , mm Hg									
CV	35 ± 1	42 ± 3	44 ± 2	45 ± 2	46 ± 3	48 ± 3	53 ± 3	49 ± 5 [§]	55 ± 5 [‡]
BV	36 ± 1	43 ± 2	48 ± 3	45 ± 4	47 ± 2	52 ± 5	52 ± 5	47 ± 4 ^{††}	45 ± 3 ^{††}
Pv _{O₂} , mm Hg									
CV	75 ± 10	46 ± 4	46 ± 3	45 ± 3	41 ± 3	38 ± 3	33 ± 4	38 ± 4 [§]	36 ± 5 [‡]
BV	80 ± 10	48 ± 4	45 ± 3	48 ± 5	47 ± 5	45 ± 6	43 ± 7	48 ± 7 ^{††}	47 ± 7 ^{††}
pH									
CV	7.42 ± 0.01	7.35 ± 0.02	7.33 ± 0.01	7.32 ± 0.01	7.31 ± 0.02	7.29 ± 0.02	7.27 ± 0.02	7.27 ± 0.03 [§]	7.24 ± 0.03 ^{‡‡}
BV	7.40 ± 0.01	7.34 ± 0.02	7.31 ± 0.02	7.32 ± 0.03	7.29 ± 0.03	7.29 ± 0.03	7.28 ± 0.04	7.33 ± 0.03 ^{††}	7.33 ± 0.03 ^{††}
Q _s /Q _T									
CV	4.3 ± 2.6	36.3 ± 9.0	42.3 ± 6.7	41.1 ± 8.4	42.7 ± 9.9	45.2 ± 9.8	47.1 ± 8.5	42.2 ± 10.9 [§]	58.9 ± 15.1 [‡]
BV	9.2 ± 3.1	42.3 ± 4.7	51.0 ± 6.5	46.4 ± 6.3	45.0 ± 6.4	46.4 ± 8.1	48.2 ± 9.3	40.9 ± 9.3 ^{††}	44.6 ± 11.8 ^{††}

Definition of abbreviations: Pa_{O₂} = arterial partial pressure of oxygen; Pa_{CO₂} = arterial partial pressure of carbon dioxide; pH = arterial blood pH; Pv_{O₂} = venous partial pressure of oxygen; Q_s/Q_T = shunt fraction.

* Values are mean ± SEM. Times are times after OA injury.

[†] p < 0.05 for differences between groups.

n = 9 except, ^{††}n = 5, [§]n = 6, ^{†††}n = 7.

Pa_{O₂} values of 89 ± 9.7 mm Hg versus 77 ± 6.4 mm Hg and shunt values of 0.36 ± 0.09 versus 0.42 ± 0.05 for the CV and BV groups, respectively, at 30 min after lung injury. In the CV group, nine, six, and five animals survived to 180, 210, and 240 min, respectively, compared with nine, seven, and seven animals in the BV group (p = 0.90).

Hemodynamic data are shown in Table 2. Some animals died before 4 h, and the means at 210 and 240 min therefore include fewer subjects, as indicated. Mean Pa, Ppao, and hemoglobin (h) were constant over the 4-h experimental period and showed no significant differences in the CV and BV groups. Ppa and Rpv increased with time in both groups. However, the two groups were not statistically different except at baseline and at 240 min. CO decreased significantly after OA injury in both groups, and remained relatively unchanged thereafter; the two groups were not statistically different in CO at any time point. Longitudinal analysis showed no differences in the time courses of hemodynamics in the BV and CV groups (Ppa: p = 0.62; Ppao: p = 0.98; Rpv: p = 0.18; CO: p = 0.99; Pa: p = 0.61).

Respiratory gas data are summarized in Table 3 and Figure 4. In both groups, Pa_{O₂} and Pv_{O₂} decreased significantly after OA injury, and were not statistically different in the two groups at any time points or over time. Pa_{CO₂} increased and pH decreased with time in both groups, but were not statistically different in the two groups. Q_s/Q_T increased significantly after OA injury, but was again not statistically different in the two groups. By longitudinal analysis, significance values were Pa_{O₂}: p = 0.77; Pv_{O₂}: p = 0.29; Pa_{CO₂}: p = 0.93; pH: p = 0.92; and shunt: p = 0.86. Figure 5 shows the Pa_{O₂} data versus time for the nine individual animals in each group.

Airway pressures, V_T, and Cst are shown in Table 4 and Figure 4. PIP and mean Paw increased significantly after OA injury and continued to increase with time, but the CV and BV groups did not differ significantly (PIP: p = 0.86; mean Paw: p = 0.68). PIP and mean Paw of individual breaths were calculated from the digitized airway pressure data and averaged over 30-min epochs after lung injury (CV group, n = 5; BV group, n = 6). Cst decreased significantly after OA injury and continued to decrease with time in both the CV and BV groups. The two groups did not differ significantly in Cst (p =

0.82). Delivered V_T was well matched between groups, and the baseline mean V_T values were maintained throughout the experiment (p = 0.18 for V_T versus time by longitudinal analysis).

DISCUSSION

The management of mechanical ventilation in patients with ARDS and ALI remains a difficult challenge because of the tradeoff between maintaining adequate gas exchange and furthering lung injury by overdistention. Some innovative approaches and adjuncts to mechanical ventilation, such as extracorporeal gas exchange (12, 13), inverse-ratio ventilation (14, 15), high-frequency ventilation (16, 17), and liquid ventilation (18) have been suggested to support gas exchange while reducing potentially injurious overdistention. The recent study of BV (3) described earlier suggested that mechanical ventilation with natural biologic variability in f and V_T could reduce lung injury and improve gas exchange without increases in mean Paw or PIP. In that study, V_T gradually decreased in both CV and BV treatment groups. It decreased more in the CV group, and this was associated with a higher Pa_{CO₂}, lower pH, and higher CO. The higher CO could have affected the key outcome variable, oxygenation. Our experiments were designed to assess effects of BV with constant tidal volumes, Pa_{CO₂}, and CO. With this approach, we found no differences between our BV and CV groups in hemodynamics, respiratory gas tensions, airway pressures, or lung mechanics. Other possible explanations for the differences in our findings and those of the study described earlier (3) include the animal models used and the BV pattern utilized.

Hemodynamic and Ventilatory Considerations

In the previous study (3), there were significantly higher mean Pa_{O₂}, lower shunt, and higher Cst values in the BV group than in the CV group. However, the CV group had higher mean Pa_{CO₂} and lower pH values, and CO was significantly higher starting at 30 min after OA injury. Although the baseline values of V_T were comparable in the CV and BV groups, mean V_T decreased with time in both groups and, more importantly, the values of V_T in the CV group became significantly smaller than those in the BV group.

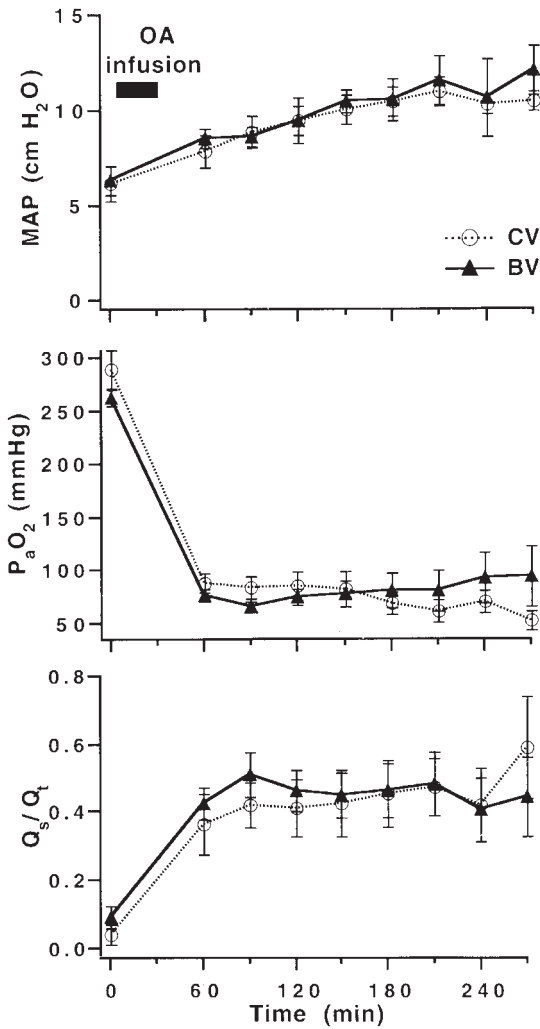


Figure 4. Time course of mean Paw, PaO₂, and Q_s/Q_t for BV and CV groups. OA was infused from time = 0 to time = 30 min. Values are means ± SEM.

Some of these results may be due in part to important differences between the ventilators used in this previous study and our study. The ventilator used in the previous study appears to have been load sensitive, so that the delivered V_T progressively decreased as compliance decreased, whereas our ventilator delivered a V_T independent of compliance. As a result, airway pressures in our animals progressively increased. Although our baseline oxygenation was similar to that in the previous study, gas exchange deteriorated during our study, whereas it stabilized or improved in the previous study. Perhaps this was caused by the higher airway pressures in the face of falling compliance in our study, leading to further ventilator induced lung injury. However, despite similar mean Paw and PIP values in our two study groups, there was no apparent salutary effect of BV. Moreover, the peak and mean pressures were lower than those known to cause ventilator-associated lung injury, and were lower than those obtained in the prior study. Nonetheless, the possibility of ventilator-induced lung injury cannot be excluded.

Differences in CO between treatment groups may also have had an effect on the shunts in the groups, a possibility recognized in the previous study. In an isolated blood-perfused dog lung lobe preparation, Sandoval and coworkers (19) showed that with a fixed P_{vO₂}, a changing CO had no immediate effect on shunt, and that with a fixed CO, shunt was linearly related

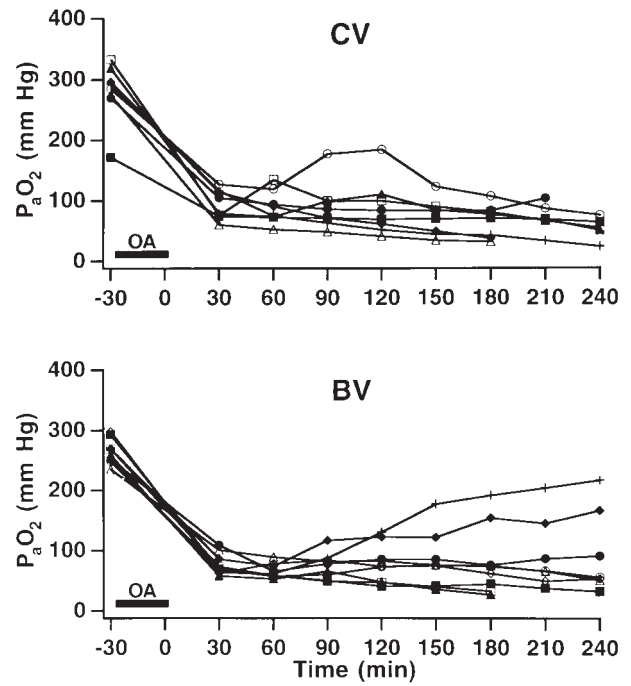


Figure 5. Time course of PaO₂ for the nine individual animals in each of the CV and BV groups.

to P_{vO₂}. They postulated that decreases in pulmonary arterial PO₂ could contribute to hypoxic pulmonary vasoconstriction, altering the distribution of pulmonary blood flow at constant CO and changing the extent of shunt. In light of this, the investigators in the previous BV study reasoned that the differences in CO observed in their experiments did not cause the differences that occurred in shunt, since the P_{vO₂} values were similar in the CV and BV groups. Thus, they attributed the improved gas exchange with BV to enhanced airway recruitment.

However, aside from the immediate influence of CO and P_{vO₂} on shunt, the development of alveolar edema after OA-induced changes in lung vascular permeability depends strongly on the level of perfusion of the injured lung regions (20, 21); a higher CO can increase shunt through worsening of lung edema (22, 23). Moreover, decreased ventilation in the CV group in the previous study of CV and BV could have contributed to the increased shunt in that group owing to the smaller delivered V_T and decreased end-inspiratory recruitment (24). Hypercarbia and acidosis may have further contributed to the higher CO found in the CV group, through reflex sympathetic stimulation. The differences in Cst in the previous study are also difficult to interpret. They may represent a beneficial effect of BV on lung recruitment, and the hypoventilation in the CV animals may have resulted from their falling compliance. Alternatively, the lower Cst may merely reflect the greater edema resulting from the higher CO, and/or decreased end-inspiratory recruitment from the decreased V_T in the CV group. Thus, smaller values of V_T, decreased ventilation, and higher CO are confounding factors that may have influenced the results of the previous study. In our experiments, V_T, PaCO₂, P_{vO₂}, and CO were well matched in the CV and BV groups, and no differences were found in the resultant PaO₂, shunt, or Cst.

BV Data Sources

A potentially important difference between the previous study of BV and our study was the source of the data used to gener-

TABLE 4
DATA FOR AIRWAY PRESSURE, TIDAL VOLUME, AND STATIC COMPLIANCE*

Parameter	Baseline	30 min	60 min	90 min	120 min	150 min	180 min	210 min	240 min
Mean Paw, cm H ₂ O									
CV [‡]	6.2 ± 0.9	7.9 ± 0.9	8.9 ± 0.8	9.5 ± 0.7	10.1 ± 0.7	10.5 ± 0.8	11.0 ± 0.7	10.3 ± 0.6 [¶]	10.5 ± 0.5 [¶]
BV [§]	6.4 ± 0.8	8.5 ± 0.5	8.6 ± 0.5	9.5 ± 1.2	10.5 ± 0.6	10.6 ± 1.1	11.6 ± 1.2	10.7 ± 2.0 [¶]	12.2 ± 1.2 [¶]
PIP, cm H ₂ O									
CV [‡]	11.8 ± 2.2	16.4 ± 1.9	18.7 ± 1.7	20.0 ± 1.4	21.1 ± 1.3	21.9 ± 1.3	22.8 ± 1.4	21.4 ± 0.7 [¶]	21.7 ± 0.7 [¶]
BV [§]	12.2 ± 2.1	16.9 ± 1.1	18.1 ± 1.2	19.6 ± 2.2	21.5 ± 1.3	21.9 ± 1.9	23.2 ± 2.2	21.9 ± 3.4 [¶]	24.3 ± 2.4 [¶]
Cst, ml/cm H ₂ O/kg									
CV	1.9 ± 0.2	1.4 ± 0.1	1.3 ± 0.1	1.2 ± 0.1	1.2 ± 0.1	1.1 ± 0.1	1.1 ± 0.1	1.1 ± 0.1 [§]	1.0 ± 0.1 [‡]
BV [†]	2.1 ± 0.1	1.3 ± 0.1	1.2 ± 0.1	1.2 ± 0.1	1.1 ± 0.1	1.1 ± 0.1	1.0 ± 0.1	1.1 ± 0.1 [‡]	1.1 ± 0.1 [‡]
Vr, ml									
CV [‡]	229 ± 34 [¶]	257 ± 26	257 ± 26	258 ± 26	255 ± 27	255 ± 27	255 ± 27	258 ± 53 [¶]	256 ± 53 [¶]
BV [‡]	243 ± 11 [¶]	284 ± 12	229 ± 23	247 ± 15	259 ± 19	254 ± 3	257 ± 20	250 ± 31 [¶]	269 ± 15 [¶]

Definition of abbreviations: Cst = static compliance; Paw = airway pressure; PIP = peak inspiratory pressure; Vr = delivered tidal volume.

* Values are mean ± SEM. Times are times after OA injury.

n = 9 except, [†]n = 8, [‡]n = 5, [§]n = 6, [¶]n = 3, [¶]n = 4.

ate the f variability files. The previous study used the peak-to-peak variability in systolic blood pressure of an anesthetized pig as the basis for the breathing f file, based on the previous demonstration that variability in heart rate, peak-to-peak changes in systolic blood pressure, and respiratory rate were similar and shared a common centering frequency equal to the respiratory f (25). In the present study, a file of actual interbreath periods, obtained from an awake, spontaneously breathing, quiescent dog was used to generate the BV breathing pattern. The frequency distributions of the f files for the two studies were similar in shape (Figure 2; [3]; Figure 2), but our file was longer (784 versus 368 breaths), and its coefficient of variation was considerably higher (24% versus 11.5%). It is possible that BV showed no advantage in our study because of differences in these f distributions. For example, improvement in alveolar recruitment implies that the net effect of volume gained during larger breaths must exceed the effect of any volume lost during smaller breaths. The larger coefficient of variation indicates that our file had more breaths below as well as above the mean, and the more numerous smaller breaths may have counteracted the benefits of the larger breaths.

Species Differences

Another potentially significant difference between the previous study and our study of BV is the animal model of pig ver-

sus that of dog. Although we adjusted our OA dose to provide a similar initial Pa_O₂ as Lefevre and colleagues, the higher mortality (six of 18 animals) and progressive deterioration in oxygenation in both of our study groups suggests a species difference that resulted in a more severe injury that was not responsive to BV.

Perhaps the most noteworthy anatomic difference between the pig and the dog is that the dog has collateral ventilation channels in the distal lung, which in the pig are virtually absent (26). These channels, which primarily connect at the level of the alveolar duct (26), provide an alternate pathway for inflation of distal lung units. Human lungs also contain collateral channels. In pathologic conditions in which airway obstruction may occur at any level of branching, collateral channels may provide a partial bypass to the obstruction and increase the number of pathways available for opening distal airways. In addition, collateral channels improve mechanical interdependence, which further supports uniform expansion of air spaces (27). When surrounding airways are partly inflated, obstructed alveolar ducts may open because tethering forces act downstream of the obstructed region. Thus, one would expect that collateral channels would facilitate the recruitment of airways and alveoli. However, since BV appeared to be more effective in the pig than the dog, the presence of collateral channels does not explain the difference in findings in the studies of BV with these two species.

However, Kuriyama and associates (28) have hypothesized that species with well-developed collateral channels (e.g., dogs) have less need for a vasoconstrictor response to hypoxia, whereas species with poorly developed collateral channels (e.g., pigs) have a greater dependence on vascular responses to maintain Pa_O₂ when airways are obstructed. As they point out, this may explain why dogs exhibit feeble pulmonary vascular responses to hypoxia as compared with pigs, and why shunts are greater in dogs than in pigs, as seen in our study and that of Lefevre and colleagues (3). Although multiple airway pathways are present and mechanical interdependence would be expected to be improved with collateral channels, a poor pulmonary vascular response to regional hypoxia in dogs may help explain the difference in findings in the two studies.

Stochastic Resonance Hypothesis

Suki and colleagues proposed a mechanism invoking the statistical phenomenon of stochastic resonance to explain the effects of BV seen in Lefevre and colleagues' study of BV (29). Because of the nonlinear shape of the PV curve of the injured lung, which

TABLE 5

COMPARISON OF DISTRIBUTIONS OF PEAK INSPIRATORY PRESSURE RELATIVE TO AIRWAY PRESSURE AT LOWER FLEXION POINT OF PRESSURE-VOLUME CURVE AMONG EXPERIMENTS WITH THEIR END ARTERIAL OXYGEN TENSIONS

Experiment	Pflex (cm H ₂ O)	Min PIP (cm H ₂ O)	Max PIP (cm H ₂ O)	Breaths with PIP	
				below Pflex (%)	End Pa _O ₂ (mm Hg)
CV 6	14.5	17	20.6	0	63.6
CV 7	16	6.9	20.3	75.4	31.8*
CV 8	14	8.3	19.9	31.7	50.5
CV 9	14	13.3	24.2	8.1	37.9*
BV 4	15.5	4.9	30.8	38.7	32.5*
BV 5	15	6.6	31.4	29.6	32.3
BV 6	17	6.6	36.1	32.9	51.2
BV 7	15	7.3	38.4	15.6	26.5*
BV 8	17	4.5	25.9	95.8	166.6
BV 9	17	5.7	29.3	52.5	53.8

Definition of abbreviations: Pflex = airway pressure at lower flexion point of pressure volume curve; PIP = peak inspiratory pressure.

* At 180 min after OA injury.

typically exhibits a change in slope about the P_{flex} point on its inspiratory limb (Figure 3), an increment in V_T above a mean value that extends above P_{flex} will cause a smaller increase in Paw than the decrease in Paw caused by a corresponding decrement in V_T. As a result, when values V_T are distributed above and below P_{flex}, the resulting mean Paw is lower than it would be for the same average V_T delivered constantly. Through this mechanism, therefore, BV could produce an increased average end-inspiratory volume and consequently increased recruitment without increases in mean Paw. It's essential, however, that the values of PIP be distributed about P_{flex} in order to take advantage of the nonlinearity of the PV curve.

Although our study was not specifically designed to investigate this hypothesis, we were able to examine the relationship between PIP and P_{flex} for our last 10 animals, using an online system in which Paw and flow of every breath were digitized for subsequent analysis. Table 5 presents the relationship between the distribution of breath PIP values relative to P_{flex} and the final PaO₂. As required by the stochastic resonance hypothesis, the majority of these animals did have their PIP values distributed about P_{flex}. Consequently, our data do not support the stochastic resonance explanation for how BV could improve recruitment and oxygenation. As intriguing as the hypothesis of Suki and colleagues appears, a ventilation scheme with a variable V_T designed to distribute PIP about P_{flex} may be of limited clinical relevance, since some clinicians and investigators recommend raising PEEP above P_{flex} to prevent ventilator-associated lung injury from repeated opening and closing of small bronchioles and alveoli (27, 30).

Variability or BV?

Although we used a BV file of dog respiratory breathing patterns, we know of no advantage of "biologic" variability over other forms of variability with respect to the explanations offered for how BV ventilation could improve recruitment and oxygenation. Both the "avalanche" model of recruitment (31) and the stochastic resonance mechanism (29) would work equally well with an arbitrarily imposed variation of appropriate size, amplitude, and distribution. Alternatively, one could speculate that, in addition to these mechanical explanations, there is a requisite reflex component to the phenomenon of recruitment that is activated only with "biologic" breathing patterns. Thus, although we did not find a benefit to BV, it could be that our pattern lacked some essential component of variability.

Conclusion

In summary, in a canine model of lung injury, we found no advantage to mechanical ventilation with f and V_T varied in a pattern derived from normal canine breathing as compared with ventilation with a constant f and V_T at equal minute volumes. The previously reported benefit of BV in pigs may reflect technical or species differences, or may be due to the lower CO in animals allocated to BV than in those given CV in the study in which this was reported. Frequent large sighs have shown transient improvement of oxygenation in ARDS (4–6). However, we found no empiric advantage to either a smaller variation in breath size and frequency or to a "natural" breathing pattern. These data suggest that BV neither aids lung recruitment nor ameliorates lung injury.

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