

Biologically Variable Ventilation Improves Oxygenation and Respiratory Mechanics during One-lung Ventilation

Michael C. McMullen, M.D., Linda G. Girling, B.Sc.,† M. Ruth Graham, M.D.,‡ W. Alan C. Mutch, M.D.§*

Background: **Hypoxemia is common during one-lung ventilation (OLV). Atelectasis contributes to the problem. Biologically variable ventilation (BVV), using microprocessors to reinstitute physiologic variability to respiratory rate and tidal volume, has been shown to be advantageous over conventional monotonous control mode ventilation (CMV) in improving oxygenation during the period of lung reinflation after OLV in an experimental model. Here, using a porcine model, the authors compared BVV with CMV during OLV to assess gas exchange and respiratory mechanics.**

Methods: **Eight pigs (25–30 kg) were studied in each of two groups. After induction of anesthesia—tidal volume 12 ml/kg with CMV and surgical intervention—tidal volume was reduced to 9 ml/kg. OLV was initiated with an endobronchial blocker, and the animals were randomly allocated to either continue CMV or switch to BVV for 90 min. After OLV, a recruitment maneuver was undertaken, and both lungs were ventilated for a further 60 min. At predetermined intervals, hemodynamics, respiratory gases (arterial, venous, and end-tidal samples) and mechanics (airway pressures, static and dynamic compliances) were measured. Derived indices (pulmonary vascular resistance, shunt fraction, and dead space ventilation) were calculated.**

Results: **By 15 min of OLV, arterial oxygen tension was greater in the BVV group (group × time interaction, $P = 0.003$), and shunt fraction was lower with BVV from 30 to 90 min (group effect, $P = 0.0004$). From 60 to 90 min, arterial carbon dioxide tension was lower with BVV (group × time interaction, $P = 0.0001$) and dead space ventilation was less from 60 to 90 min (group × time interaction, $P = 0.0001$). Static compliance was greater by 60 min of BVV and remained greater during return to ventilation of both lungs (group effect, $P = 0.0001$).**

Conclusions: **In this model of OLV, BVV resulted in superior gas exchange and respiratory mechanics when compared with CMV. Improved static compliance persisted with restoration of two-lung ventilation.**

OPTIMAL management of one-lung ventilation (OLV) remains a challenge in how best to adequately oxygenate the patient, without excessive airway pressures. Atelectasis contributes to the gas exchange problems seen during OLV. Under experimental conditions, reinflation of a collapsed lung after OLV was facilitated when positive-pressure ventilation was delivered using a variable respiratory rate and tidal volume, resulting in better oxygenation and respiratory system compliance.[1] This experiment was one in a series where so-called biologically variable ventilation (BVV) was compared with conventional control mode ventilation (CMV), with BVV demonstrating superior gas exchange and respiratory mechanics in porcine models of acute respiratory distress syndrome, with and without positive end-expiratory pressure,[2,3] and during prolonged anesthesia in healthy lungs.[4] In a recent clinical trial, BVV showed improved gas exchange during abdominal aortic aneurysmectomy.[5]

Whether BVV could offer any improvement over CMV in gas exchange or respiratory mechanics while the dependent lung is ventilated during OLV and after return to two-lung ventilation remains unexplored. Here, we describe a porcine model of OLV comparing the two ventilatory approaches.

Materials and Methods

Surgical Preparation

This study was approved by the University of Manitoba Protocol Review Committee (Winnipeg, Manitoba, Canada). Healthy, fasted pigs (25–30 kg) were premedicated with an intramuscular injection of atropine–midazolam–ketamine (0.02/0.5/10 mg/kg) before undergoing a mask induction with 5% isoflurane in oxygen. When an adequate depth of anesthesia was obtained, the animals were intubated with a 6.5-mm cuffed endotracheal tube, and mechanical ventilation was initiated using an Ohio 7000 anesthesia ventilator (Ohmeda, Rexdale, Ontario, Canada). Anesthesia was maintained with 2.0% isoflurane in oxygen during surgical preparation. Neuromuscular blockade was achieved with pancuronium (0.2 mg/kg) and maintained throughout the study by continuous infusion (10 mg/h). A 7-French catheter was inserted after cut-down in the femoral artery for blood gas and hemodynamic monitoring. A 7.5-French pulmonary artery thermodilution catheter was advanced into the proximal pulmonary artery for measurement of mixed venous gases, pressures, temperature, and cardiac output (Edwards COM2; Carlsbad, CA). A pneumotachometer (Hans Rudolph 3700B series; Kansas City, MO) and carbon dioxide sensor (NICO 3700; Novametrics, Wallingford, CT) were placed distal to the Y-connector of the

* Senior Resident, † Senior Technician, Anesthesia Research Laboratory, ‡ Associate Professor, § Professor.

Received from the Department of Anesthesia, Health Sciences Centre, University of Manitoba, Winnipeg, Manitoba, Canada. Submitted for publication November 29, 2005. Accepted for publication March 29, 2006. Supported by the Canadian Institutes of Health Research, Ottawa, Ontario Canada; The James S. McDonnell Foundation, St. Louis, Missouri; and The Dean's Fund, Winnipeg, Manitoba, Canada. Dr. Mutch is Cofounder and Vice President of Research, Biovar Life Support Inc., Winnipeg, Manitoba, Canada, the company founded to license and market biologically variable ventilation (BVV) discussed in this article. Worldwide exclusive rights to BVV have been issued to Respironics Inc., Vista, California. If BVV is successfully marketed, Dr. Mutch stands to gain financially from sales. Respironics did not fund this project, nor did they have any input into the design, conduct of the experiment, interpretation of the data, writing of the manuscript, or decision on where to submit the manuscript for publication. In the past, Respironics has provided funding for research projects done in the laboratory. No other author stands to gain financially from the sale of BVV.

Address correspondence to Dr. Mutch: Anesthesia Research Laboratory, A-504 Chown Building, 744 Bannatyne Avenue, Winnipeg, Manitoba, Canada. amutch@cc.umanitoba.ca.

respiratory circuit to record respiratory mechanics and carbon dioxide partial pressures, respectively. A bolus of lactated Ringer's solution was administered to obtain central venous pressure greater than 3 mmHg. During the course of the experiment, fluid administration was limited to an infusion of 1.5 ml · kg^{-1} · h^{-1}.

To facilitate lung isolation, a tracheostomy was secured with a 9.0-mm internal diameter cuffed endotracheal tube. The volatile agent was then discontinued, and the anesthetic was converted to a standardized total intravenous technique using propofol (10 mg · kg^{-1} · h^{-1}) and ketamine (2.5 mg · kg^{-1} · h^{-1}). An alveolar recruitment maneuver (30 cm H_2O for 30 s) was performed before the animals were switched to an Esprit ventilator (Respironics, Vista, CA), capable of delivering either BVV or CMV, with a tidal volume of 12 ml/kg, a respiratory rate of 20 breaths/min, a positive end-expiratory pressure of 5 cm H_2O, and a fractional inspired oxygen concentration of 1.0.

Blood Gases and Respiratory Mechanics

Arterial and mixed venous gases were analyzed by a blood gas machine (Radiometer ABL500; Copenhagen, Denmark). Arterial and mixed venous oxygen content, saturation, and hemoglobin concentration were measured by a hemoximeter set for porcine blood (Radiometer OSM3). All blood gas samples were measured and results reported at 37°C. Respiratory system static compliance was measured in triplicate by the occlusion method at end inspiration. Plateau pressures were measured 1 s after occlusion. Volume–pressure loops were constructed and analyzed by area. Dynamic compliance was calculated as the slope between times of zero flow in the volume–pressure loops. After a 15-min period of stabilization, baseline hemodynamics, respiratory mechanics, and analysis of arterial, mixed venous, and end-tidal gases were obtained. All baseline measurements were repeated after a reduction in the tidal volume to 9 ml/kg and adjustment in respiratory rate to maintain end-tidal carbon dioxide tension less than 50 mmHg and arterial pH greater than 7.30.

One-lung Ventilation Protocol

Lung isolation was achieved using an Arndt endobronchial blocker (Cook Critical Care, Bloomington, IN) positioned in the animal's left main-stem bronchus under fiberoptic bronchoscope guidance (Olympus CLK-3; Melville, NY). Before the onset of OLV, the animal was randomly assigned to either BVV (treatment group) or continued CMV (control group). The introduction of biologic variability was controlled *via* a laptop computer, RS-232 cabled to the Esprit ventilator. For both CMV and BVV, a square wave inspiratory flow pattern was chosen. The inspiratory to expiratory duty cycle was 1:2 for both modes of ventilation. The variability algorithm with alterations in respiratory rate and tidal volume was adjusted to ensure the same minute ventilation as with CMV as previously described.[6] This variability file has been previously shown to have fractal characteristics with a fractal dimension of 1.27 as assessed by relative dispersion analysis.[7] While in BVV mode, the ventilator functioned as a volume divider. Minute ventilation remained fixed (respiratory rate × tidal volume product was constant); an increase in rate was accompanied by a proportional decrease in tidal volume to maintain fixed minute ventilation—*vice versa* for a decrease in rate. If in BVV mode, airway and hemodynamic data were collected for more than 350 breaths to accurately determine mean airway pressure and mean peak airway pressure due to the breath-by-breath variation in tidal volume. The positive end-expiratory pressure was removed before the onset of OLV. To ensure adequate collapse of the left lung, an expiratory hold (10 s) was performed before inflation of the blocker with 6–8 ml of air. The position and adequacy of the blocker seal was confirmed with the bronchoscope by two investigators immediately after inflation and again, once the animal was positioned in the right lateral decubitus position. A thoracotomy incision was then performed, and adequacy of lung isolation was confirmed by direct visualization of the collapsed left lung.

Oxygenation was monitored with arterial and venous blood gases obtained at 5, 15, 30, 60, and 90 min after the onset of OLV. Hemodynamics and respiratory mechanics, including respiratory system static and dynamic compliance, were recorded at 30-min intervals throughout the study. At completion of 90 min of OLV, adequate lung isolation was again confirmed before removal of the endobronchial blocker. Gradual inflation of the left lung was achieved with an alveolar recruitment maneuver by momentarily switching to the Ohio 7000 anesthesia ventilator with continuous positive airway pressure (30 cm H_2O for 30 s). Return to the Esprit ventilator followed with application of positive end-expiratory pressure of 5 cm H_2O. Ventilation of both lungs was maintained for 60 min before the animals were killed. A midline sternotomy was performed, and the lungs were inspected for evidence of gross pathology before excision for calculation of wet-to-dry weight ratios.

Statistical Analysis

Parametric data were analyzed by repeated-measures analysis of variance. Group effects and group × time interactions were examined. If these were significantly different by F statistic, $P \leq 0.05$, then least squares means test matrices were examined to identify differences within and between groups. The Bonferroni correction for multiple comparisons was applied when appropriate. A P value of 0.05 or less corrected for multiple comparisons was considered significant.

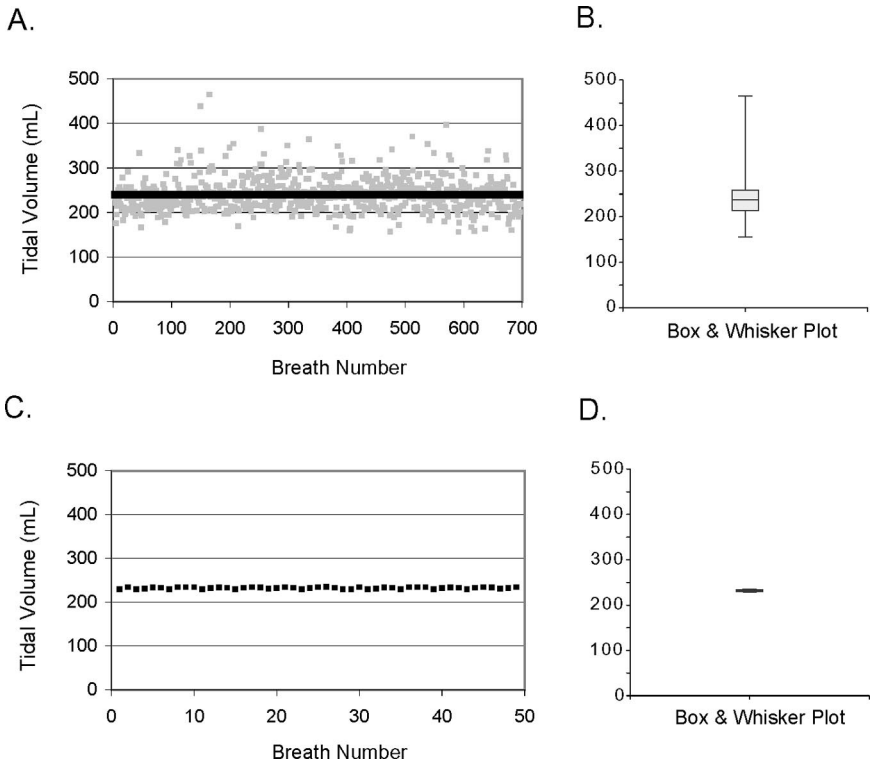

Fig. 1. Single experiment tidal volume plots for biologically variable ventilation and control mode ventilation. (*A*) Tidal volume over 700 breaths during one-lung ventilation in one animal receiving biologically variable ventilation. Mean tidal volume, shown by *dark line*, was 240 ml. (*B*) Box and whisker plot of the same data show median, first and third quartiles, and overall range in this animal. (*C*) Tidal volume over 50 breaths during one-lung ventilation in one animal receiving control mode ventilation. Mean tidal volume was 227 ml. (*D*) Box and whisker plot of the same data in this animal.

Results

The model of OLV was successfully applied in all 16 animals studied (n = 8 per group). Lung isolation with the endobronchial blocker was achieved in all animals and confirmed by both fiberoptic and direct visualization. When ventilated at 12 ml/kg, the two groups did not differ in respiratory mechanics or gas exchange before randomization, and these results are not further commented on. The institution of biologic variability during OLV introduced breath-by-breath variation in tidal volume and respiratory rate (fig. 1) at essentially the same minute ventilation as seen in the CMV group.

Temperature changes and hemodynamic measurements during the course of the experiment are shown in table 1. At baseline, there was no difference in temper-

Table 1. Temperature and Hemodynamics

	Baseline before OLV	OLV 30 min	OLV 60 min	OLV 90 min	TLV 30 min	TLV 60 min
Temp						
BVV	36.9 ± 0.5	36.4 ± 0.9	36.3 ± 0.9	36.3 ± 1.0*	36.3 ± 1.3*	36.2 ± 1.4*
CMV	37.0 ± 0.6	37.1 ± 0.7†	37.1 ± 0.7†	37.2 ± 0.6†	37.2 ± 0.9†	37.2 ± 1.0†
MAP						
BVV	99 ± 11	108 ± 7	113 ± 8*	118 ± 12*	120 ± 14*	118 ± 19*
CMV	94 ± 11	109 ± 7*	114 ± 24*	117 ± 21*	116 ± 21*	123 ± 17*
MPAP						
BVV	20.2 ± 2.6	27.8 ± 3.3*	28.3 ± 3.6*	27.4 ± 4.4*	23.1 ± 4.6	22.4 ± 6.0
CMV	22.0 ± 5.5	30.0 ± 6.1*	31.9 ± 6.6*	31.3 ± 3.6*	25.1 ± 3.1	25 ± 2.1
CO						
BVV	4.3 ± 1.3	5.0 ± 1.4	4.5 ± 0.9	4.2 ± 0.8	2.9 ± 0.8*	3.1 ± 1.0*
CMV	5.3 ± 0.9†	5.3 ± 1.4	4.8 ± 1.3	4.1 ± 1.4*	3.1 ± 1.5*	3.2 ± 1.4*
PAOP						
BVV	10.4 ± 1.8	9.6 ± 3.2	10.5 ± 3.5	9.8 ± 4.1	9.6 ± 2.2	8.9 ± 2.7
CMV	9.6 ± 2.6	9.2 ± 3.7	9.6 ± 4.1	10.0 ± 4.0	10.6 ± 2.4	9.8 ± 1.6
PVR						
BVV	2.4 ± 0.5	3.8 ± 0.8*	4.3 ± 0.9*	4.4 ± 1.1*	5.1 ± 2.0*	5.1 ± 2.6*
CMV	2.5 ± 1.1	4.0 ± 0.8*	4.8 ± 1.4*	5.5 ± 1.6*	5.3 ± 1.5*	5.2 ± 1.3*

* $P < 0.05$ within groups *versus* baseline. † $P < 0.05$ between groups.

BVV = biologically variable ventilation; CMV = control mode ventilation; CO = cardiac output (l/min); MAP = mean arterial pressure (mmHg); MPAP = mean pulmonary artery pressure (mmHg); OLV = one-lung ventilation; PAOP = pulmonary artery occlusion pressure (mmHg); PVR = pulmonary vascular resistance ($mmHg \cdot l^{-1} \cdot min^{-1}$); Temp = temperature (°C); TLV = two-lung ventilation.

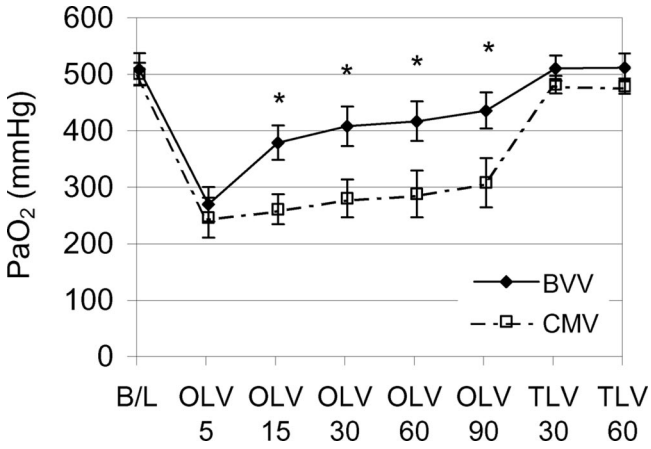

Fig. 2. Arterial oxygen tension (Pao_2) *versus* time for the two experimental groups, biologically variable ventilation (BVV) and control mode ventilation (CMV). By 15 min of one-lung ventilation (OLV), arterial oxygen tension was greater with BVV that persisted out to 90 min ($P = 0.003$, group × time interaction). * $P < 0.05$ between groups at specified time periods. TLV = two-lung ventilation. B/L = baseline.

ature between groups. By 30 min of OLV, the core temperature was greater in animals in the CMV group, which persisted for the remainder of the experiment. With institution of OLV, mean arterial pressure and mean pulmonary artery pressure increased in both groups but were not different between groups. Baseline cardiac output was higher in the control group (5.3 ± 0.9 *vs.* 4.3 ± 1.3 l/min; $P = 0.05$); however, this difference was not maintained at subsequent time periods. Pulmonary vascular resistance increased in both groups with OLV and remained increased for the remainder of the experiment (not significantly different between groups).

Marked reductions in arterial oxygen tensions were observed in both groups 5 min after the onset of OLV ($P = 0.003$, group × time interaction). By 15 min, oxygenation was consistently higher in the BVV group for the duration of OLV (fig. 2). Differences between groups resolved with reinstitution of two-lung ventilation.

Table 2 shows respiratory gas and derived data. By 60 min of OLV, the arterial carbon dioxide tension was greater in the CMV group compared with the BVV group ($P = 0.0001$, group × time interaction). These differences resolved with two-lung ventilation. A marked increase in the arterial to end-tidal carbon dioxide difference was seen with initiation of OLV in both groups. Between-group differences were also seen at 60 and 90 min of OLV, with the gradient being significantly less in the BVV group ($P = 0.016$, group × time interaction). In both groups, mixed expired carbon dioxide tension increased with OLV, but no differences were seen between groups. The increase in both groups resolved with two-lung ventilation. Dead space ventilation also differed significantly ($P = 0.0001$, group × time interaction), with dead space significantly higher at 60 and 90 min with CMV. Shunt fraction markedly increased in both groups with OLV ($P = 0.0004$, group effect). Significant differences were seen between the two groups

Table 2. Respiratory Gas and Derived Data

	Baseline before OLV	OLV 30 min	OLV 60 min	OLV 90 min	TLV 30 min	TLV 60 min
pHa						
BVV	7.38 ± 0.04	7.34 ± 0.04*	7.35 ± 0.03*	7.35 ± 0.03*	7.38 ± 0.03*	7.38 ± 0.03*
CMV	7.39 ± 0.04	7.32 ± 0.03*	7.30 ± 0.05*†	7.29 ± 0.06*†	7.35 ± 0.05*	7.35 ± 0.05*
P_{VO_2}						
BVV	56.6 ± 6.3	60.9 ± 5.0	61.7 ± 5.2*	59.0 ± 5.0	51.5 ± 7.5	51.0 ± 6.9
CMV	59.9 ± 5.2	60.5 ± 6.8	56.3 ± 3.0†	55.7 ± 4.1	50.0 ± 3.4*	49.5 ± 5.5*
Pa_{CO_2}						
BVV	47.3 ± 4.6	53.6 ± 6.2*	53.5 ± 3.2*	52.2 ± 2.8*	49.1 ± 3.3	48.1 ± 3.9
CMV	46.1 ± 3.9	54.4 ± 4.5*	58.5 ± 6.3*†	59.5 ± 9.3*†	50.5 ± 5.2*	49.1 ± 3.7
Pa_{CO_2}–ET_{CO_2}						
BVV	0.3 ± 2.7	4.9 ± 3.1*	5.1 ± 2.7*	4.9 ± 3.0*	1.0 ± 3.6	0.8 ± 4.6
CMV	−1.6 ± 2.4	7.5 ± 6.3*	9.6 ± 6.8*†	8.9 ± 8.2*†	0.7 ± 2.3	0.6 ± 1.9
P_{ECO_2}						
BVV	16 ± 4	19 ± 3*	19 ± 3*	19 ± 3*	16 ± 3	16 ± 4
CMV	17 ± 2	18 ± 2*	19 ± 2*	19 ± 2*	17 ± 3	17 ± 3
Q_S/Q_T						
BVV	9.0 ± 5.7	16.2 ± 6.2*	15.7 ± 7.2*	13.0 ± 5.3*	6.8 ± 3.9	6.4 ± 3.8
CMV	10.3 ± 4.3	22.0 ± 5.9*†	19.9 ± 8.0*†	17.1 ± 8.7†	7.1 ± 2.9	6.9 ± 2.6
V_D/V_T						
BVV	67.4 ± 5.5	64.3 ± 4.0	64.5 ± 5.1	64.5 ± 5.5	67.3 ± 7.2	66.7 ± 8.2
CMV	64.1 ± 4.8	66.6 ± 4.1	67.7 ± 4.3†	67.5 ± 4.8†	65.8 ± 4.3	65.7 ± 4.9

* $P < 0.05$ within groups *versus* baseline. † $P < 0.05$ between groups.

BVV = biologically variable ventilation; CMV = control mode ventilation; OLV = one-lung ventilation; Pa_{CO_2} = arterial partial pressure of carbon dioxide (mmHg); Pa_{CO_2}–ET_{CO_2} = arterial partial pressure of carbon dioxide to end-tidal carbon dioxide gradient (mmHg); P_{ECO_2} = mixed expired partial pressure of carbon dioxide(mmHg); P_{VO_2} = mixed venous oxygen tension (mmHg); Q_S/Q_T = shunt fraction (%); TLV = two-lung ventilation; V_D/V_T = physiologic dead space ratio (%).

Table 3. Respiratory Mechanics

	Baseline before OLV	OLV 60 min	TLV 60 min
Peak P_{aw}			
BVV	14.8 ± 1.8	17.3 ± 2.0*	17.1 ± 1.1*
CMV	15.0 ± 1.7	21.8 ± 2.4*†	19.8 ± 2.2*†
Mean P_{aw}			
BVV	7.4 ± 1.6	3.7 ± 0.5*	8.2 ± 0.3*
CMV	7.6 ± 0.5	4.3 ± 0.6*	8.6 ± 0.4*
V_T			
BVV	9.0 ± 0.2	8.3 ± 0.4*	8.5 ± 0.4*
CMV	9.1 ± 0.1	8.4 ± 0.3*	8.5 ± 0.3*
MV			
BVV	5.5 ± 0.8	5.3 ± 0.6	5.2 ± 0.7
CMV	5.5 ± 0.3	5.2 ± 0.2	5.2 ± 0.3
Crs_{dyn}			
BVV	0.88 ± 0.16	0.49 ± 0.07*	0.79 ± 0.15*
CMV	0.91 ± 0.21	0.37 ± 0.05*†	0.64 ± 0.18*†

* $P < 0.05$ within groups *versus* baseline. † $P < 0.05$ between groups.

BVV = biologically variable ventilation; CMV = control mode ventilation; Crs_{dyn} = dynamic compliance (ml · cm H_2O^{-1} · kg^{-1}); Mean P_{aw} = mean airway pressure (cm H_2O); MV = minute ventilation (l/min); OLV = one-lung ventilation; Peak P_{aw} = peak airway pressure (cm H_2O); TLV = two-lung ventilation; V_T = tidal volume (ml/kg).

from 30 to 90 min of OLV. Differences resolved with restoration of two-lung ventilation.

Respiratory mechanics are noted in table 3. Significant differences were seen between the two ventilation strategies for several measures. During the period of OLV, the expected increases in mean peak inspiratory pressures were seen with OLV, even with the removal of 5 cm H_2O positive end-expiratory pressure. The increase in mean peak inspiratory pressure was attenuated with BVV compared with CMV. Peak pressures remained higher when measured at 60 min after restoration of two-lung ventilation. The group × time interaction for mean peak inspiratory pressure was $P = 0.0001$. In contrast, mean airway pressure was significantly lower with OLV from baseline—a consequence of the loss of positive end-expiratory pressure. At 60 min of two-lung ventilation, the mean airway pressure was higher than at baseline in both groups, and not different between groups. As designed, no differences in tidal volume or minute ventilation were seen between groups. Measured tidal volume during OLV averaged 8.4 ± 0.3 ml/kg with CMV and 8.3 ± 0.4 ml/kg with BVV. Dynamic compliance was significantly higher with BVV during OLV and return to two-lung ventilation ($P = 0.011$, group × time interaction).

Baseline respiratory system static compliance was 36.3 ± 6.4 ml/cm H_2O at a mean weight of 27.3 ± 1.4 kg in animals receiving CMV and 34.6 ± 2.3 ml/cm H_2O at 27.8 ± 1.4 kg with BVV. Static compliance (reported as ml · cm H_2O^{-1} · kg^{-1}) was higher in the animals receiving BVV during OLV and the subsequent return to ventilation of both lungs ($P = 0.0001$, group effect; fig. 3). Representative dynamic volume–pressure loops during OLV are shown for animals receiving BVV and CMV (fig. 4). The area of the volume–pressure loop was constructed and analyzed at baseline and at 60 min of OLV. At baseline, both groups had similar curves (loop area = 1,175 ± 167 *vs.* 1,203 ± 178 ml · cm H_2O; $P = 0.76$), whereas during OLV, the BVV group had a significantly smaller loop area (1,964 ± 311 *vs.* 2,220 ± 162 ml · cm H_2O; $P = 0.05$).

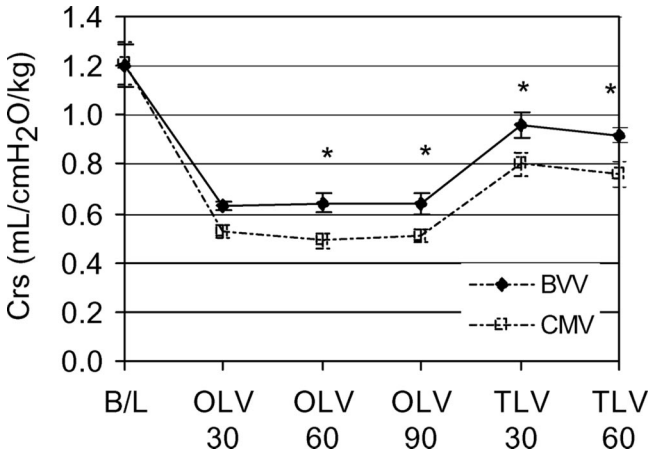

Fig. 3. Respiratory system static compliance (Crs) *versus* time for the two experimental groups, biologically variable ventilation (BVV) and control mode ventilation (CMV). By 60 min, Crs was greater with BVV. This effect persisted with return to two-lung ventilation (TLV). OLV = one-lung ventilation. * $P < 0.05$ between groups at specified time periods. B/L = baseline.

No differences were seen in the wet-to-dry weight ratios between the two ventilation strategies (BVV, 5.5 ± 0.5 *vs.* CMV, 5.6 ± 0.4).

Discussion

One-lung ventilation has assumed a vital role in facilitating modern thoracic surgical procedures in a patient

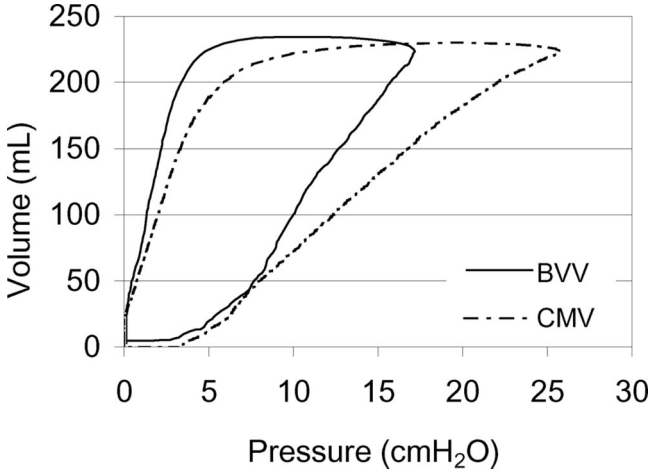

Fig. 4. Volume–pressure loops from two representative experiments at 60 min of one-lung ventilation. At the same tidal volume, loop area was greater with control mode ventilation (CMV; 2,460 ml · cm H_2O) compared with biologically variable ventilation (BVV; 2,070 ml · cm H_2O). The inspiratory flow characteristics at these similar representative tidal volumes are identical between the two ventilator modes.

population with significant respiratory comorbidities. The onset of OLV is characterized by the development of a significant intrapulmonary shunt through the collapsed lung with the potential for intraoperative hypoxemia. The dependent lung is subjected to the gravitational effects of lateral positioning and surgical compression with the resultant atelectasis further contributing to the magnitude of the shunt during lung isolation. During OLV, the dependent lung is susceptible not only to significant atelectasis but also to increased airway pressures. In this experiment, we have shown that introduction of biologic variability during OLV significantly improves both oxygenation and respiratory mechanics. Previous work had shown that BVV was superior to either CMV or CMV with sigh breaths in recruiting collapsed lung units after OLV,[1] was superior to recruitment maneuvers with CMV for maintaining oxygenation at lower tidal volumes in models of acute respiratory distress syndrome,[6] and provided superior gas exchange compared with CMV in a model of prolonged anesthesia.[4]

Application of BVV significantly reduced the shunt fraction and improved oxygenation during ventilation of the dependent lung. Within 15 min of onset of OLV, arterial oxygen tensions were higher with BVV, and this effect persisted throughout the period of intervention. BVV may be attenuating segmental atelectasis in the dependent lung and thereby better preserving functional ventilation/perfusion ratios. Given the limitations of current methods to treat hypoxemia during OLV (continuous positive airway pressure to nondependent lung or return to two-lung ventilation), any technique that preserves oxygenation may be welcomed in clinical practice. The ability of positive end-expiratory pressure applied to the dependent lung to improve oxygenation is not uniformly advantageous, and benefit, if present, may be influenced by the patient's baseline forced expiratory volume in 1 s.[8,9] A cost of positive end-expiratory pressure is increased airway pressure to the dependent lung.

Tusman *et al.*[10] used an alveolar recruitment strategy to improve oxygenation during OLV (mean arterial oxygen tension 144 mmHg before the alveolar recruitment strategy *vs.* 244 mmHg after the strategy). The improvement was attributed to recruitment of atelectatic regions in the dependent lung during OLV. The recruitment strategy of Tusman *et al.* involved peak airway pressures of 40 cm H_2O and positive end-expiratory pressures of 20 cm H_2O to overcome critical opening pressures. This approach increases the potential for barotrauma and required high central venous pressure (> 10 mmHg) to avoid adverse hemodynamic effects. With BVV used during OLV, oxygenation was improved and alveolar ventilation increased without increased airway pressures or adverse hemodynamic effects. BVV has been compared with similar alveolar recruitment strategies in animal models and has been shown to be superior.[1,6]

The arterial carbon dioxide to end-tidal carbon dioxide tension gradient is an indirect index of shunt and alveolar dead space.[11] This gradient increased dramatically with the onset of OLV and to a significantly greater extent in animals ventilated with CMV compared with those receiving BVV. This finding concurs with greater dead space ventilation at 60 and 90 min with CMV. No significant difference in mixed expired carbon dioxide tension was seen between groups. The same mixed expired carbon dioxide tension in the face of a greater arterial carbon dioxide tension and dead space ventilation can indicate a greater shunt or high ventilation/perfusion ratio or a combination of both during CMV at the same mean tidal volume.[12] Supporting the interpretation of a higher ventilation/perfusion ratio is the lower respiratory system dynamic compliance at similar tidal volume with CMV during OLV and greater work of breathing as evidenced by the area of the volume–pressure loop (fig. 4). During OLV, greater driving pressure would preferentially distribute airflow to the nondependent regions—regions characteristically with a higher ventilation/perfusion ratio. A complete understanding of the forces at work here will require a breath-by-breath analysis of the carbon dioxide expirogram.[13] To truly compare the variable tidal volumes inherent with BVV to the monotonous tidal volume with CMV will require analysis of a sufficient number of BVV breaths so that mean tidal volume over the interval of interest is identical to that with CMV. The current experiment has data averaged over minute intervals—mean 25 breaths/min. This resolution is not adequate to define per breath carbon dioxide volume expired—true alveolar ventilation with each exhalation, nor do the current data permit a breakdown into separate components of the expirogram necessary to fully analyze the problem—separate determinations of alveolar ventilation, alveolar dead space ventilation, physiologic dead space, and apparatus dead space.

The improvements in respiratory mechanics seen with the introduction of variability extend beyond a reduction in airway pressure. Respiratory system static compliance is a reflection of the distending forces applied at the alveolar level. The improvement in static compliance seen with BVV supports the concept that this ventilatory strategy was able to recruit more alveoli in the dependent lung during OLV. This improvement in alveolar recruitment has been seen in several previous experiments from our laboratory during two-lung ventilation.[1,2,6] Examination of the dynamic volume–pressure curves during OLV (fig. 4) demonstrates considerably more distortion with CMV compared with BVV. Sigmoidal volume–pressure loops, similar to those seen in the control animals, have been documented in a previous human trial of OLV.[14] Peak airway pressures were lower with BVV at 60 min OLV, but there was no difference in lung wet-to-dry weight ratios seen between groups, indicating no significant differences in lung water.

Lower core temperatures were seen within 30 min of initiating OLV that persisted. We have observed lower core

temperatures when ventilating with BVV compared with CMV in models of acute respiratory distress syndrome.[15] The nature of this difference remains to be elucidated.

Of note is that the beneficial respiratory mechanics seen with BVV persisted after reinstitution of two-lung ventilation. Respiratory system static and dynamic compliance were both greater after reexpansion of the collapsed lung with a uniform recruitment maneuver out to 60 min—the end of the experiment. Lower mean peak airway pressures were seen with BVV after return to two-lung ventilation.

We have recently demonstrated mathematically the conditions under which the addition of noise to the end inspiratory pressure signal, as with BVV, can be advantageous.[16] When the volume–pressure curve is convex curvilinear, as occurs with OLV in the lateral position,[8] BVV is advantageous with its noisy inspiratory pressure over the monotonous inspiratory pressure that occurs with CMV. The optimal "noisy" signal to use with BVV is as yet unknown. We have advanced the suggestion that fractal noise as used in this study may offer some advantages to "white" or random noise.[16] In health, physiologic signals can usually be demonstrated to be mono or even multifractal.[17–19] Fractal signals are "colored" noise and have autocorrelation, meaning in the context under discussion that a large tidal volume will be followed by a second large tidal volume with a probability greater than chance. The same probability characteristics also apply to small tidal volumes. The variability file used to program the ventilator while in BVV mode was obtained from a healthy, spontaneously breathing human volunteer. This file has a fractal dimension of 1.27 analyzed using the approach of Glenny *et al.*[7] By way of comparison, a completely monotonous signal has a dimension of 1.00 and a "white" noise signal a dimension of 1.50 (no autocorrelation over time).[7] Recent work by Bellardine *et al.*[20] provides insight into why the large tidal volumes with variable ventilation recruit collapsed lung. In their study using a saline lavage model, recruitment associated with a large tidal volume could last for more than 200 s, which was nearly an order of magnitude greater than the mean time interval between large tidal volume breaths in their variability file.

A recognized limitation of this study is that we used healthy animals without any underlying respiratory disease as opposed to the considerable respiratory pathology typically present in patients undergoing pulmonary resection. However, we believe our model is clinically relevant, because the changes observed in oxygenation in the control group closely resemble those seen in a previous clinical study.[21] BVV has previously been applied successfully during the perioperative period,[5] and we would not anticipate undue technical difficulties in using a BVV strategy in patients undergoing thoracotomy in future clinical trials.

Traditional anesthetic management during OLV has focused on hypoxic pulmonary vasoconstriction and methods to provide adequate oxygenation. Few clinicians have approached the problem with a focus on the ventilation strategy applied to the dependent lung. By adding biologic variability to the positive pressure delivered to the dependent lung during OLV, oxygenation and respiratory mechanics were improved. BVV may potentially provide anesthesiologists with a ventilation strategy to improve intraoperative management of patients requiring OLV.

References

1. Mutch WAC, Harms S, Graham MR, Kowalski SE, Girling LG, Lefevre GR: Biologically variable or naturally noisy mechanical ventilation recruits atelectatic lung. Am J Respir Crit Care Med 2000; 162:319–23
2. Mutch WAC, Harms S, Lefevre GR, Graham MR, Girling LG, Kowalski SE: Biologically variable ventilation increases arterial oxygenation over that seen with positive end-expiratory pressure alone in a porcine model of acute respiratory distress syndrome. Crit Care Med 2000; 28:2457–64
3. Lefevre GR, Kowalski SE, Girling LG, Thiessen DB, Mutch WAC: Improved arterial oxygenation after oleic acid lung injury in the pig using a computer-controlled mechanical ventilator. Am J Respir Crit Care Med 1996; 154:1567–72
4. Mutch WAC, Eschun GM, Kowalski SE, Graham MR, Girling LG, Lefevre GR: Biologically variable ventilation prevents deterioration of gas exchange during prolonged anaesthesia. Br J Anaesth 2000; 84:197–203
5. Boker A, Haberman CJ, Girling L, Guzman RP, Louridas G, Tanner JR, Cheang M, Maycher BW, Bell DD, Doak GJ: Variable ventilation improves perioperative lung function in patients undergoing abdominal aortic aneurysmectomy. ANESTHESIOLOGY 2004; 100:608–16
6. Funk DJ, Graham MR, Girling LG, Thliveris JA, McManus BM, Walker EK, Rector ES, Hillier C, Scott JE, Mutch WAC: A comparison of biologically variable ventilation to recruitment manoeuvres in a porcine model of acute lung injury. Respir Res 2004; 5:22
7. Glenny RW, Robertson HT, Yamashiro S, Bassingthwaighte JB: Applications of fractal analysis to physiology. J Appl Physiol 1991; 70:2351–67
8. Valenza F, Ronzoni G, Perrone L, Valsecchi M, Sibilla S, Nosotti M, Santambrogio L, Cesana BM, Gattinoni L: Positive end-expiratory pressure applied to the dependent lung during one-lung ventilation improves oxygenation and respiratory mechanics in patients with high FEV_1. Eur J Anaesthesiol 2004; 21:938–43
9. Slinger PD, Kruger M, McRae K, Winton T: Relation of the static compliance curve and positive end-expiratory pressure to oxygenation during one-lung ventilation. ANESTHESIOLOGY 2001; 95:1096–102
10. Tusman G, Böhm SH, Vazquez de Anda GF, do Campo JL, Lachmann B: "Alveolar recruitment strategy" improves arterial oxygenation during general anaesthesia. Br J Anaesth 1999; 82:8–13
11. Nunn JF: Distribution of pulmonary ventilation and perfusion, Applied Respiratory Physiology, 4th edition. Oxford, Butterworth-Heinemann, 1993, pp 156–97
12. West JB: Distribution of pulmonary blood flow. Am J Respir Crit Care Med 1999; 160:1802–3
13. Anderson CT, Breen PH: Carbon dioxide kinetics and capnography during critical care. Crit Care 2000; 4:207–15
14. Bardoczky GI, Levarlet M, Engelman E, deFrancquen P: Continuous spirometry for detection of double-lumen endobronchial tube displacement. Br J Anaesth 1993; 70:499–502
15. Boker A, Graham MR, Walley KR, McManus BM, Girling LG, Walker E, Lefevre GR, Mutch WAC: Improved arterial oxygenation with biologically variable or fractal ventilation using low tidal volumes in a porcine model of acute respiratory distress syndrome. Am J Respir Crit Care Med 2002; 165:456–62
16. Brewster JF, Graham MR, Mutch WAC: Convexity, Jensen's inequality and benefits of noisy mechanical ventilation. J R Soc Interface 2005;2:393–6
17. Goldberger AL, West BJ: Fractals in physiology and medicine. Yale J Biol Med 1987; 60:421–35
18. Ivanov PC, Amaral LAN, Goldberger AL, Havlin S, Rosenblum MG, Struzik ZR, Stanley HE: Multifractality in human heartbeat dynamics. Nature 1999; 399: 461–5
19. Mutch WAC, Lefevre GR: Health, "small-worlds," fractals and complex networks: An emerging field. Med Sci Monit 2003; 9:M19–23
20. Bellardine CL, Hoffman AM, Tsai L, Ingenito EP, Arold SP, Lutchen KR, Suki B: Comparison of variable and conventional ventilation in a sheep saline lavage lung injury model. Crit Care Med 2006; 34:439–45
21. Guenoun T, Journois D, Silleran-Chassany J, Frappier J, D'Attellis N, Salem A, Safran D: Prediction of arterial oxygen tension during one-lung ventilation: Analysis of preoperative and intraoperative variables. J Cardiothorac Vasc Anesth 2002; 16:199–203