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Variable Ventilation Improves Perioperative Lung Function in Patients Undergoing Abdominal Aortic Aneurysmectomy

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Background: **Optimizing perioperative mechanical ventilation remains a significant clinical challenge. Experimental models indicate that "noisy" or variable ventilation (VV)—return of physiologic variability to respiratory rate and tidal volume—improves lung function compared with monotonous control mode ventilation (CV). VV was compared with CV in patients undergoing abdominal aortic aneurysmectomy, a patient group known to be at risk of deteriorating lung function perioperatively.**

Methods: **After baseline measurements under general anesthesia (CV with a tidal volume of 10 ml/kg and a respiratory rate of 10 breaths/min), patients were randomized to continue CV or switch to VV (computer control of the ventilator at the same minute ventilation but with 376 combinations of respiratory rate and tidal volume). Lung function was measured hourly for the next 6 h during surgery and recovery.**

Results: **Forty-one patients for aneurysmectomy were studied. The characteristics of the patients in the two groups were similar. Repeated-measures analysis of variance (group × time interaction) revealed greater arterial oxygen partial pressure ($P = 0.011$), lower arterial carbon dioxide partial pressure ($P = 0.012$), lower dead space ventilation ($P = 0.011$), increased compliance ($P = 0.049$), and lower mean peak inspiratory pressure ($P = 0.013$) with VV.**

Conclusions: **The VV mode of ventilation significantly improved lung function over CV in patients undergoing abdominal aortic aneurysmectomy.**

THE transition from awake, spontaneous breathing to the anesthetized state with spontaneous breathing in the supine position and the further transition to being paralyzed and mechanically ventilated introduce profound physiologic changes. With induction of anesthesia and mechanical ventilation in the supine position, patients quickly develop areas of dependent atelectasis with proportional right-to-left shunting.[1] Anesthesia and mechanical ventilation also result in reduction in functional residual capacity to a point approaching or below closing capacity. The resulting airway closure may contribute to the dependent atelectasis, low ventilation/perfusion ($\dot{V}_A/\dot{Q}$) ratios, and possibly some of the compliance changes seen during anesthesia.[2] The overall result is an impairment of gas exchange with potential hypoxemia during anesthesia with mechanical ventilation. Patients undergoing abdominal surgery with placement of mechanical retractors and abdominal packs seem to be particularly prone to these complications.

Modern mechanical ventilators operating in control mode deliver respiratory rate (RR) and tidal volume (V_T) in a monotonously regular manner. In contrast, normal ventilation is characterized by a variable or "noisy" signal.[3] Most if not all physiologic signals manifest variability of a specific type. When transformed and displayed graphically, such signals plot as a straight line that mathematically describes a simple power law.[4] Variable or noisy time sequences are associated with health, and their loss often heralds premorbid deterioration.[5,6]

With modern mechanical ventilators, microprocessors examine each breath to ensure constant volume is delivered by compliance compensation algorithms. If a change to a more monotonous signal is associated with deteriorating health, it is possible that life support could be improved with return of a noisy signal to the device output. Mutch *et al.*,[7–11] using a porcine model ventilated with variable RR and V_T, a mode termed *biologically variable ventilation*, have presented experimental evidence supporting this contention, and there is independent confirmation from Arold *et al.*[12] in a rodent model. Suki *et al.*[13] has offered theoretical proof of the beneficial effect of noise in biologic life-support systems, specifically as it relates to this mode of ventilation.

Our intention with this pilot study was to examine, in a clinical setting, a novel mode of mechanical ventilation with demonstrable efficacy in several animal models of pulmonary pathophysiology. In this study, a ventilator designed to deliver noisy or variable ventilation (VV), *i.e.*, variable RR and V_T, was compared with monotonous control mode ventilation (CV) in patients undergoing abdominal aortic aneurysmectomy. Patients such as these, with upper abdominal incisions and the need for abdominal packs and retraction, are at particular risk of experiencing deteriorating lung function during laparotomy. We chose this group of patients to be studied because we have found them to develop a measurable (but not critical) defect in pulmonary gas exchange, and we believed they represented a group most likely to reveal efficacy of any experimental intervention. We looked specifically at a comparison of CV with VV to

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determine whether there were any differences in pulmonary gas exchange, respiratory mechanics, or radiographic evidence of atelectasis.

Materials and Methods

The Health Research Ethics Board at the University of Manitoba (Winnipeg, Canada) approved this study. All patients were recruited and studied at a single institution (University of Manitoba). Patients scheduled to undergo elective abdominal aortic aneurysmectomy were identified, and those eligible were approached for recruitment at the time of their visit to the preanesthetic clinic. Informed consent was obtained at the time of recruitment. Exclusion criteria were chronic congestive heart failure, unstable angina, morbid obesity (body mass index > 35), significant chronic obstructive pulmonary disease (forced expiratory volume in 1 s < 1.0 l), bullous emphysema, severe asthma, previous thoracic surgery, drug or alcohol abuse, and pregnancy. Women with childbearing potential were also excluded. Patients continued their medications except oral hypoglycemics, hepatic 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, anticoagulants, and at times, antiplatelet therapy. Patients were maintained on therapy for insulin-dependent diabetes, angina, hypertension, and chronic obstructive pulmonary disease.

Estimation of Sample Size

A conventional sample size calculation was problematic because we did not have clinical data for VV. We arbitrarily chose a sample size of 20 patients/group in this pilot clinical study of VV.

Intraoperative Management

All patients received a large-bore intravenous cannula, an intraarterial cannula for continuous monitoring of blood pressure and for arterial blood gas analysis, and an internal jugular cannula to assess intravascular volume. A high lumbar or low thoracic epidural catheter was inserted, through which patients received a continuous infusion of 0.06 mg/ml bupivacaine and 30 μg/ml hydromorphone, initiated on induction of anesthesia and continued throughout the duration of the 6-h study and afterward for pain control. Anesthesia consisted of propofol, sufentanil, and rocuronium, initially given as intravenous bolus doses and then infused continuously (total intravenous anesthesia). An intensive care ventilator (Respironics, Inc., Carlsbad, CA) was used in both arms of the study. Initial settings were a V_T of 10 ml/kg (ideal body weight), and a RR of 10 breaths/min in CV mode with zero end-expiratory pressure, an inspiratory: expiratory ratio of 1:2, and an inspired oxygen fraction (F_{IO_2}) of 0.6. If arterial carbon dioxide partial pressure (P_{aCO_2}) was not 35–45 mmHg, RR was adjusted. At 20 min after intubation, baseline measures of gas exchange included arterial oxygen partial pressure (P_{aO_2}), P_{aCO_2}, pH, and mixed expiratory gas. Respiratory variables were determined with use of pneumotachography (Hans Rudolph Linear Bi-Directional Pneumotach model 3700; Hans Rudolph, Inc., Kansas City, MO), with the sensor positioned at the proximal end of the endotracheal tube, connected to a custom-designed pressure and flow measurement device, and included mean airway pressure (P_{aw}), mean peak inspiratory (PIP), airway plateau pressure, and V_T.

After determination of baseline measurements, patients were randomly allocated to receive either CV or VV. Randomization was determined by drawing an envelope from a pool of 40 identical, unmarked, sealed envelopes, half containing CV designation and half containing VV designation. The envelopes were thoroughly shuffled to ensure selection was truly random. A second set of measurements was obtained 20 min after randomization. The time of insertion of abdominal packs and retractor was recorded, and every effort was made to coordinate this with the measurement intervals such that the intervention occurred immediately after a measurement time. Measurements were obtained at hourly intervals thereafter for the duration of the 6-h study period. The time in the operating room was noted. Because of the obvious differences in RR and V_T with CV and VV, blinding of the research personnel and attending physicians was not possible.

Surgical Management

The abdominal aorta was exposed by means of a paramedian incision. Abdominal contents were displaced with packs after positioning of a mechanical retractor. Before cross clamping of the abdominal aorta, 6,000 U heparin and 25 g mannitol were administered. Aortic reconstruction was by knitted polyester tube graft or bifurcated aortobifemoral graft. Standard abdominal wound closure was undertaken.

Postoperative Management

Sufentanil infusion was discontinued after wound closure. At the end of surgery, patients were transferred to either the postanesthesia recovery room or the surgical intensive care unit. The criterion for transfer to either the postanesthesia recovery room or the surgical intensive care unit was based on the need for extended (*i.e.*, overnight) invasive monitoring or mechanical ventilation. Early postoperative management (*i.e.*, first 4–5 h) was otherwise the same in all patients, irrespective of which unit they recovered in. In the sixth hour, the propofol dose was tapered. At 6 h, the propofol and rocuronium infusions were stopped. Muscle relaxation was reversed with intravenous glycopyrrolate and neostigmine. A supine chest radiograph was obtained. Patients were weaned from mechanical ventilation ac-

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cording to standard protocols. If mechanical ventilation remained necessary, CV was used. One hour after extubation, arterial blood gas measurements were taken. The next day, the chest radiography and arterial blood gas measurements were repeated. This represented the study endpoint. At any time, at the discretion of the attending physician, the study could be terminated if patient welfare was considered to be compromised.

Variable Ventilation

The ventilator delivered a square-wave inspiratory flow pattern and, in VV mode, functioned as a volume divider (changes in RR resulted in reciprocal changes in V_T for any given set of dialed-in parameters). For VV, a laptop computer program was engaged to deliver the same minute ventilation as with CV but was controlled by a modulation file with 376 different RRs. The RR control file comes from Mutch's group (biologically variable ventilation) and is derived from data in awake, spontaneously breathing dogs. This file was stored in normalized format so that specific mean RR and V_T could be chosen to control Pa_{CO_2}. During ventilation in VV mode, a mean V_T of 10 ml/kg (ideal body weight) was delivered, with minimum and maximum V_Ts of 6.4 and 14.6 ml/kg, respectively.

Post Hoc *Analysis*

The data file of airway pressure and flow was processed to integrate the area under the pressure–time and expiratory flow–time curves to give P_{aw} and V_T. PIP was also calculated. Static respiratory system compliance (Crs) was determined over 3–5 breaths by means of measurement of airway pressure at end inspiration during 1.0- to 2.0-s clamping of the expiratory limb of the ventilator circuit (plateau pressure). The mean value was reported. Because of the variability in rate and V_T with VV, 30 min of data collection was performed at each measurement period to accurately determine mean rate, V_T, and airway pressures. Calculated indices included oxygen index ($F_{IO_2} \cdot P_{aw} \cdot 100/Pa_{O_2}$), dead space ventilation ((Pa_{CO_2} − partial pressure mixed expired carbon dioxide)/Pa_{CO_2}), and alveolar to arterial oxygen difference.

Statistical Analysis of Patient Data

Demographic data were analyzed by means of Wilcoxon rank sums and chi-square test. Hemodynamic, blood gas, and respiratory mechanics data were analyzed by repeated-measures analysis of variance. We set the α error at 0.05 for significance of group × time (G × T) interactions or differences between groups. Least-squares means test matrices were generated for *post hoc* comparisons. The Bonferroni correction was applied for multiple comparisons within groups. Single comparisons between groups were performed by means of the Student *t* test, with $P < 0.05$ considered significant. Intraoperative comparison of Pa_{O_2} and compliance slopes after the nadir with pack insertion was performed with use of analysis of covariance. A G × T of pooled slope comparison was made between groups; $P < 0.05$ was considered significant.

Radiologic Assessment of Atelectasis Postoperatively

Two radiologists who were blinded to the treatment groups assessed the 1-h and 24-h postoperative chest radiographs independently. An established atelectasis scoring system was used as follows: 0 = no atelectasis; 1 = plate-like atelectasis; 2 = segmental atelectasis; 3 = partial lobar collapse; 4 = complete lobar collapse.[14] Each lung was graded separately for a combined total maximal score of 8. The scores from each of the radiologists were compared and results were analyzed by means of the Mantel-Haenszel trend test.

Results

Forty-one patients were studied, 21 receiving CV and 20 VV (fig. 1). Thirty-eight patients completed the 6-h study. One patient in the CV group was removed from the study by the attending anesthesiologist 1 h into the protocol because the patient had gross hypoxemia and was initially unresponsive to lung volume recruitment maneuvers, and F_{IO_2} increased to 1.0. Data from this patient were not analyzed, and the randomization envelope was resealed and returned to the pool. One patient in the CV group had an unintended extubation at 5 h that necessitated reintubation, and the study was terminated for this patient. One patient in the VV group had an unintended extubation at 4 h into the study. The study was terminated when the patient was reintubated. Both of these patients were included in data analysis up until the time of extubation.

Demographics for the two groups are shown in table 1. There were no significant differences between groups for any of the variables examined. Hemodynamic parameters are shown in table 2. No clinically relevant differences were seen between groups.

The changes in Pa_{O_2} over the 6 h of perioperative management for the two groups are shown in figure 2. Repeated-measures analysis of variance demonstrated a G × T interaction of $P = 0.011$. Intergroup comparisons showed differences at 3, 4, and 5 h. Other respiratory gas analyses are shown in table 3. Significant differences between groups were seen for Pa_{CO_2} (G × T; $P = 0.012$), dead space ventilation (G × T; $P = 0.011$), and alveolar to arterial oxygen difference (G × T; $P = 0.027$). All differences favored VV. Minute ventilation was increased from baseline in 5 of 20 patients in the CV group by increasing rate, without changing V_T, to control Pa_{CO_2} (G × T; $P = 0.008$). Only 1 patient in the VV group needed a change in rate. No differences were seen in arterial pH.

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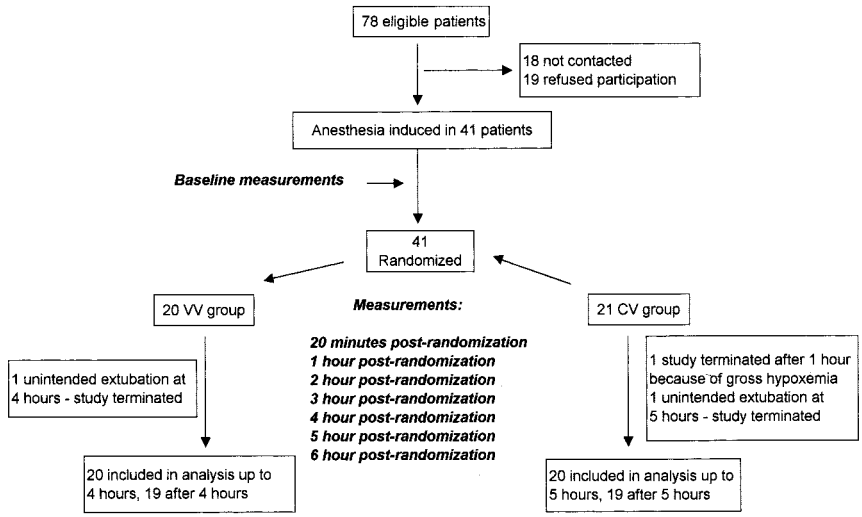

Fig. 1. Trial profile. CV = conventional mode ventilation; VV = variable ventilation.

The changes in respiratory mechanics are shown in table 4. PIP, (G × T; $P = 0.013$); Crs (G × T; $P = 0.002$) and oxygen index (G × T; $P = 0.038$) differed between groups. There was no difference in P_{aw} between groups.

Intraoperative Pa_{O_2} and Crs were examined in greater detail because time to insertion of abdominal packs and retraction differed and the intraoperative time course varied significantly among patients (fig. 3). With increasing duration of pack placement, the behavior of the two groups differed markedly. By covariant analysis, the slope of the line for Pa_{O_2} or compliance was examined from time 0 on insertion of abdominal packs. The longer the packs were in place, the greater the difference was, with Pa_{O_2} greater by almost 100 mmHg in the VV group at 3 h after retraction (G × T; $P = 0.0001$), as shown in figure 4. A similar analysis revealed increasing Crs in the VV group over time (G × T; $P = 0.0001$; fig. 5).

Examination of chest radiographs revealed no differences in severity of atelectasis between groups. Arterial blood gas measurements taken after extubation and on postoperative day 1 were not controlled for F_{IO_2} (supplemental oxygen was routinely applied), so no meaningful analysis could be undertaken; however, all patients maintained an arterial oxygen saturation (Sa_{O_2}) of greater than 90% after extubation and on postoperative day 1.

Table 1. Demographic Data

	VV	CV
Age, yr	69.6 ± 10.8	69.5 ± 7.9
Weight, kg	80.1 ± 14.1	80.8 ± 14.5
BMI, kg/m^2	27.3 ± 3.8	27.1 ± 4.1
FEV_1, l	2.14 ± 0.74	2.16 ± 0.62
FVC, l	2.80 ± .85	2.88 ± 0.92
Sex		
F	6	6
M	14	14
Smoking history		
Y	6	10
N	3	1
Quit	11	9
ASA physical status		
II	6	4
III	12	16
IV	2	0
Surgeon		
1	7	9
2	5	5
3	8	6

Demographic data for 40 patients undergoing abdominal aortic aneurysmectomy (mean ± SD). There were no differences in demographic variables in those patients ventilated with variable ventilation (VV) compared with conventional mode ventilation (CV).

ASA = American Society of Anesthesiologists.

Discussion

This is the first clinical study showing that incorporation of variability into the output of a mechanical ventilator results in improvement in measures of pulmonary function. The reintroduction of variability in RR and V_T, characteristic of normal breathing, was achieved with microprocessor control of the ventilator output. Multiple indices of improved lung function were present in the VV group, including higher Pa_{O_2}, decreased Pa_{CO_2}, reduced dead space ventilation, and improved Crs. The result was improved lung function in the VV group intraoperatively and in the early postoperative period for patients undergoing abdominal aortic aneurysmectomy. Patients such as these are known to be at risk of impaired lung function because of prolonged anesthesia and the retraction required for surgical exposure.[2]

Tokics *et al.*[1] concluded that dependent atelectasis was the major cause of impairment of gas exchange during anesthesia and mechanical ventilation. In the current study, shunt fraction was not calculated; however, the differences in Pa_{O_2} and alveolar to arterial oxygen difference between the treatment groups indicate superior $\dot{V}_A/\dot{Q}$ matching in the VV group. This preservation of $\dot{V}_A/\dot{Q}$ in VV patients may be secondary to a reduction in

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Table 2. Hemodynamic and Temperature Data

	Baseline	20 min	1 h	2 h	3 h	4 h	5 h	6 h
Esophageal temperature, °C								
VV	35.7 ± 0.5	35.6 ± 0.5	35.7 ± 0.6	35.7 ± 0.6	35.8 ± 0.7	36.0 ± 0.7*	36.2 ± 0.8*	36.3 ± 0.8*
CV	35.6 ± 0.4	35.5 ± 0.6	35.6 ± 0.5	35.8 ± 0.7	35.9 ± 0.5*	36.0 ± 0.5*	36.0 ± 0.4*	36.2 ± 0.3*
MAP, mmHg								
VV	82 ± 14	79 ± 16	82 ± 13	76 ± 11	80 ± 11	76 ± 10	80 ± 11	78 ± 10
CV	81 ± 16	74 ± 13	80 ± 8	78 ± 10	76 ± 10	81 ± 11	81 ± 10	79 ± 8
CVP, mmHg								
VV	10 ± 3	10 ± 3	9 ± 4	11 ± 3	11 ± 3	11 ± 2	11 ± 2	11 ± 3
CV	10 ± 4	11 ± 4	10 ± 4	11 ± 4	12 ± 5*	12 ± 3	12 ± 4	12 ± 4
HR, beats/min								
VV	60 ± 12	62 ± 14	61 ± 13	60 ± 11	61 ± 10	57 ± 10	58 ± 12	59 ± 13
CV	55 ± 15	58 ± 11	55 ± 9†	58 ± 11	59 ± 11	57 ± 8	57 ± 7	60 ± 9

Hemodynamic data for 40 patients undergoing abdominal aortic aneurysmectomy (mean ± SD). Baseline measurements were taken on conventional mode ventilation (CV), and then the patients were randomized to variable ventilation (VV) or CV. Subsequent measurement periods were 20 min, and hourly to 6 h after randomization. There were no clinically significant differences in hemodynamic variables or body temperature in those patients ventilated with VV compared with CV.

* $P < 0.05$ within groups compared with baseline. † $P < 0.05$ between groups.

CVP = central venous pressure; MAP = mean arterial pressure.

the severity of atelectasis, but we cannot say this definitively. Respiratory compliance decreased progressively in the CV group but remained relatively stable in the VV group. This would be consistent with more severe atelectasis in the CV group. A difference in severity of atelectasis between the treatment groups on the basis of the chest radiograph was not seen and not really expected because the duration of the surgery and anesthesia was relatively short (6 h) and the extent of atelectasis seen on chest radiograph in similar patients at our institution is modest. Computed tomography may have provided a more sensitive means of detecting differences in atelectasis between the groups. There was a modest increase in P_{aw} and PIP in the CV group over the course of the experiment that was not seen in the VV group. This did not translate into intergroup differences. It is possible that changes in airway pressures could result in redistribution of pulmonary blood flow to areas of reduced ventilation, partially accounting for the differences in Pa_{O_2} and alveolar to arterial oxygen difference between the treatment groups.

Other indices of improved alveolar ventilation are evident with VV. Pa_{CO_2} was lower, confirming previous results in experimental models of lung injury.[9] This improvement occurred despite significantly lower minute ventilation at similar body mass index with VV. VV significantly reduced dead space ventilation in this experiment, consistent with the use of biologically variable ventilation in animal experimental models of anesthesia and acute respiratory distress syndrome.[9,10] VV was associated with a lower oxygen index in this study, although it was low in both groups, indicating relatively healthy lungs in the study population as compared with acute respiratory distress syndrome.

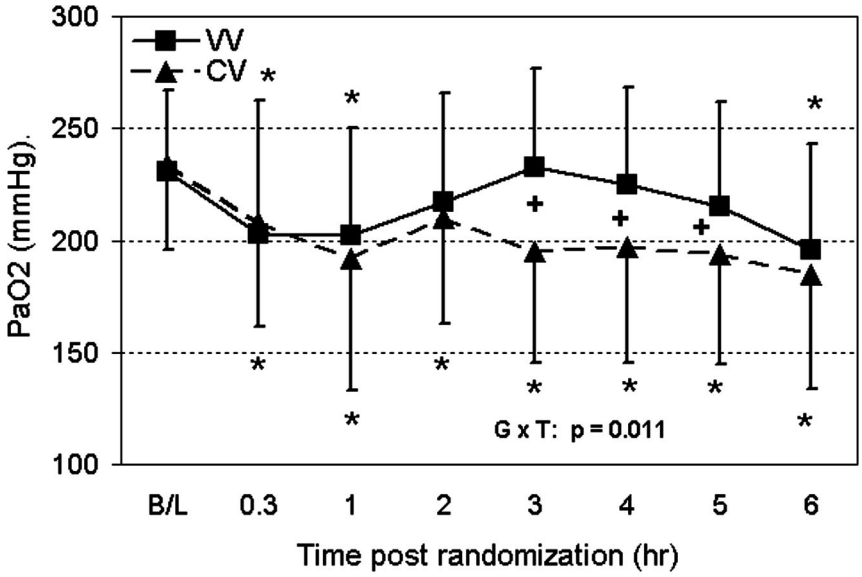

Fig. 2. Arterial oxygen partial pressure (Pa_{O_2}) (mean ± SD) for the two groups. The repeated-measures analysis of variance revealed a group × time interaction (G × T) of $P = 0.011$. * Within groups, Pa_{O_2} was lower at all time periods after baseline (B/L) measurement in the conventional mode ventilation (CV) group (corrected for multiple comparisons). With variable ventilation (VV), Pa_{O_2} was lower at 20 min and at 1 and 6 h. + Between-group comparisons showed Pa_{O_2} to be lower in the VV group at 3, 4, and 5 h.

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Table 3. Respiratory Gas Data

	Baseline	20 min	1 h	2 h	3 h	4 h	5 h	6 h
Pa_{CO_2}, mmHg								
VV	38.2 ± 3.5	36.5 ± 3.4	34.3 ± 4.5*	36.5 ± 3.9	36.4 ± 4.4	36.8 ± 3.6	36.6 ± 3.6	37.5 ± 3.8
CV	38.2 ± 3.7	36.5 ± 3.1	35.7 ± 4.6*	35.7 ± 4.0*	39.6 ± 5.1†	38.3 ± 3.4	37.3 ± 3.2	37.7 ± 4.1
pHa								
VV	7.39 ± 0.03	7.40 ± 0.03	7.40 ± 0.04	7.37 ± 0.06	7.39 ± 0.06	7.39 ± 0.06	7.40 ± 0.05	7.39 ± 0.04
CV	7.38 ± 0.04	7.39 ± 0.03	7.38 ± 0.04	7.37 ± 0.05	7.34 ± 0.07	7.38 ± 0.05	7.39 ± 0.04	7.39 ± 0.04
V_D/V_T, %								
VV	37.5 ± 3.5	35.9 ± 3.4	33.6 ± 4.6*	35.8 ± 3.9	35.7 ± 4.4	36.1 ± 3.7	35.9 ± 3.6	36.9 ± 3.9
CV	37.5 ± 3.7	35.9 ± 3.2	35.0 ± 4.6*	35.0 ± 3.4*	38.9 ± 5.2†	37.6 ± 3.5	36.6 ± 3.3	37.0 ± 4.1
A-a O_2 gradient								
VV	135 ± 35	165 ± 59*	169 ± 45*	152 ± 47	135 ± 41	143 ± 42	153 ± 46	171 ± 47*
CV	132 ± 37	160 ± 47*	178 ± 57*	160 ± 46*	169 ± 48*†	170 ± 0*†	170 ± 50*†	182 ± 50*
$\dot{V}_E$, l/min								
VV	7.7 ± 1.1	7.7 ± 1.1	7.7 ± 1.1	7.7 ± 1.1	7.7 ± 1.1	7.8 ± 1.1	7.7 ± 1.1	7.7 ± 1.1
CV	7.6 ± 0.9	7.6 ± 0.9	7.6 ± 0.9	7.6 ± 0.8	7.7 ± 1.1	8.0 ± 1.0*	8.1 ± 1.3*†	8.1 ± 1.4*†

Respiratory gas data for 40 patients undergoing abdominal aortic aneurysmectomy and ventilated using either variable ventilation (VV) or conventional mode ventilation (CV) (mean ± SD). Baseline measurements were taken on CV, and then the patients were randomized to VV or CV. Subsequent measurement periods were 20 min, and hourly to 6 h after randomization.

* $P < 0.05$ within groups compared with baseline. † $P < 0.05$ between groups.

A-a O_2 gradient = alveolar to arterial oxygen difference; Pa_{CO_2} = arterial carbon dioxide partial pressure; pHa = arterial pH; V_D/V_T = dead space:tidal volume ratio; $\dot{V}_E$ = minute ventilation.

Improvements in pulmonary function were most obvious intraoperatively. Wound retraction and packing of the upper abdomen could limit diaphragm movement and contribute to those factors producing basilar atelectasis. With removal of the abdominal packs, this specific contribution to $\dot{V}_A/\dot{Q}$ mismatching would be relieved. The examination of the intraoperative Pa_{O_2} and Crs reveals that the longer the intraoperative period is, the greater the differential between VV and CV with respect to gas exchange and compliance is. If the abdominal packs were in place for 3 h, Pa_{O_2} and Crs were markedly different between groups. With cross clamp release, other causes of impaired oxygenation may come into play, including changes in $\dot{V}_A/\dot{Q}$ associated with hypovolemia. The failure to show a significantly better Pa_{O_2} at 6 h in the VV group may, in part, be due to these factors.

This study was designed to determine whether the introduction of variability into RR and V_T would, by itself, result in improvement in pulmonary function in a clinical setting. With this in mind, we attempted to control as many variables as possible while maintaining a clinical scenario in which there would be sufficient pathophysiology to make meaningful measurements. It can be argued that many of the pulmonary abnormalities seen in the CV group might have been reduced with the institution of positive end-expiratory pressure (PEEP), sighs, or previously described recruitment maneuvers.[15] PEEP alone may diminish atelectasis during anesthesia but does not necessarily reduce shunting and improve oxygenation.[1] PEEP also increases PIP and P_{aw}. It is possible that the continued deterioration of gas exchange in both study groups beyond 5 h could have

Table 4. Respiratory Mechanics

	Baseline	1 h	3 h	6 h
P_{aw}, cm H_2O				
VV	5.0 ± 1.1	5.1 ± 0.8	4.9 ± 0.8	5.3 ± 1.3
CV	4.8 ± 1.0	5.3 ± 1.1*	5.1 ± 1.1	5.3 ± 0.8*
PIP, cm H_2O				
VV	18.5 ± 3.4	19.8 ± 2.4	18.6 ± 2.7	19.7 ± 4.4
CV	17.7 ± 3.7	21.7 ± 4.6*†	19.9 ± 3.8*	20.7 ± 3.2*
Crs, ml · cm H_2O^{-1} · kg^{-1}				
VV	0.62 ± .14	0.51 ± .10*	0.62 ± .17	0.59 ± .14
CV	0.62 ± .15	0.50 ± .14*	0.54 ± .13*†	0.55 ± .13*†
Oxygen index, cm H_2O/mmHg				
VV	1.3 ± 0.3	1.6 ± 0.5*	1.3 ± 0.3	1.6 ± .5*
CV	1.2 ± 0.4	1.9 ± 0.8*	1.7 ± 0.6*†	1.8 ± 0.7*

Respiratory mechanics data for 40 patients undergoing abdominal aortic aneurysmectomy and ventilated using either variable ventilation (VV) or conventional mode ventilation (CV) (mean ± SD). Baseline measurements were taken on CV and then the patients were randomized to VV or CV. Subsequent measurement periods were 20 min, and hourly to 6 hr after randomization.

* $P < 0.05$ within groups compared with baseline. † $P < 0.05$ between groups.

Crs = respiratory system compliance; P_{aw} = mean airway pressure; PIP = mean peak inspiratory pressure.

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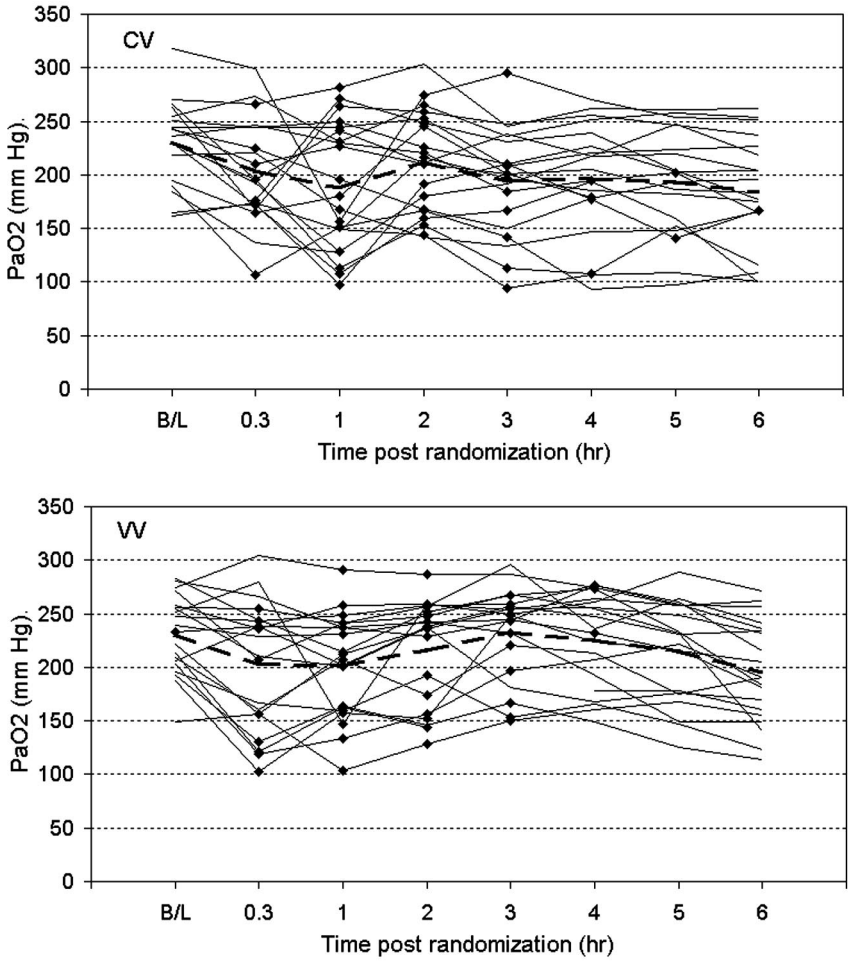

Fig. 3. Arterial oxygen partial pressure (Pa_{O_2}) values for individual patients during the course of the 6-h experiment. The *top panel* shows the conventional mode ventilation (CV) group (20 patients), and the *bottom panel* shows the variable ventilation (VV) group (20 patients). The mean value for each is represented by the *beavy dashed line*. For each experiment, measurements taken while abdominal packs and retractors were in place are represented by *diamonds*, and all data points after the last diamond are from the postoperative period.

been partially ameliorated by the institution of a small amount of PEEP.

Is VV just CV with the addition of sighs? Could this account for the improvements in pulmonary function seen with VV in this study? With VV, the maximum single breath size is 14.6 ml/kg (approximately 146% of baseline). Sighs of this frequency and magnitude have not been shown to improve Crs or gas exchange.[16] Mutch *et al.*[8] confirmed this in their animal model. Specific alveolar recruitment strategies have been described that will improve arterial oxygenation during anesthesia.[15,17] Tusman *et al.*[15] described a strategy of stepped

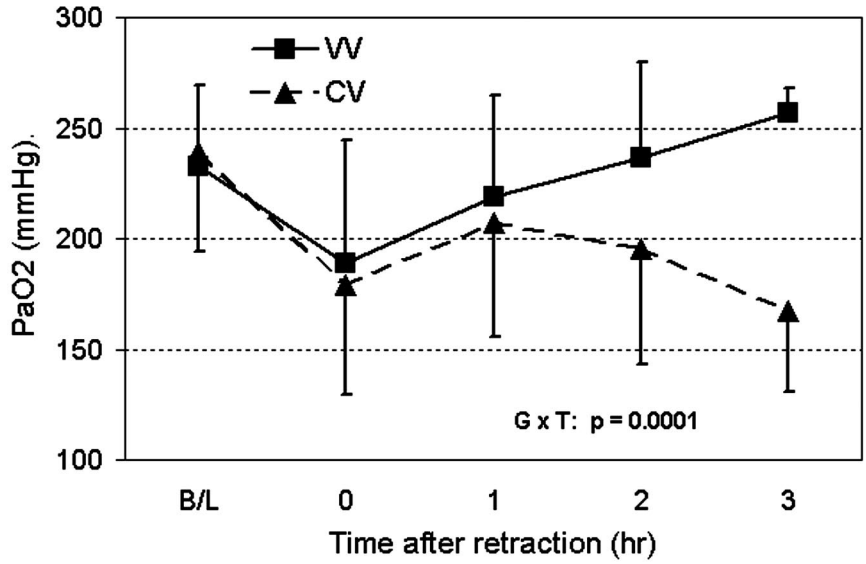

Fig. 4. Arterial oxygen partial pressure (Pa_{O_2}) (mean ± SD) at time after initiation of retraction and packing of abdominal contents. Baseline measurement decreased to time 0, *i.e.*, with insertion of retractor and abdominal packs. Covariate analysis − slope of the line for Pa_{O_2} over time from time 0 was compared within and between groups. A positive slope with a group × time interaction (G × T) of $P = 0.0001$ was seen for the variable ventilation (VV) group. The G × T for slope with the conventional mode ventilation (CV) group was $P = 0.07$. Comparison of slopes had a P value of 0.0001. When packs were present at 3 h, Pa_{O_2} was nearly 100 mmHg greater in the VV group.

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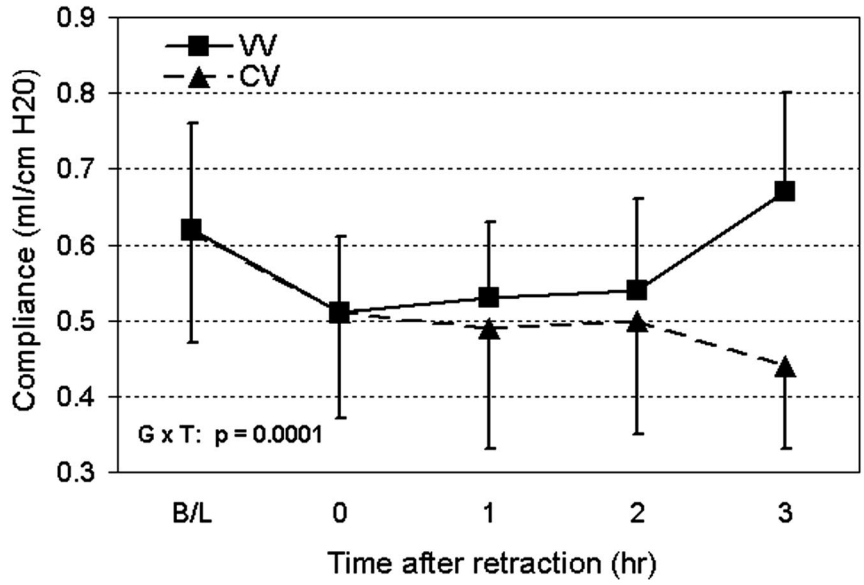

Fig. 5. Respiratory system compliance (mean ± SD) at time after initiation of retraction and packing of abdominal contents. Baseline measurements decreased to time 0, *i.e.*, with insertion of retractor and abdominal packs. Covariate analysis – slope of the line for respiratory system compliance over time from time 0 was compared within and between groups. A positive slope with a group × time interaction (G × T) of $P = 0.0001$ was seen for the variable ventilation (VV) group. The G × T for slope with conventional ventilation (CV) was $P = 0.09$. Comparison of slopes had a P value of 0.0001.

increases in V_T (up to 18 ml/kg) over a 6-min cycle, followed by PEEP (5 cm H_2O). That such recruitment strategies are effective cannot be argued. We did not propose to compare VV to an optimal mode of ventilation for this particular patient population but rather to ascertain whether VV was efficacious and whether it warranted head-to-head comparison with a previously determined "optimal" ventilation strategy. It is possible that a comparable improvement in gas exchange in these patients could have been achieved by the use of periodic large ventilations alone (*i.e.*, "sighs") in the absence of other variability in RR and V_T. By definition, this would result in an increase in P_{aw} as compared with VV. Clearly, the only way to resolve this is a head-to-head comparison of optimal ventilation techniques.

The file used to program RR and V_T in the VV group consisted of data obtained from an awake, spontaneously breathing, chronically instrumented dog. Relative dispersion analysis of the rate file[8] reveals a power law behavior with a correlation coefficient (R^2) of 0.98. Such a mathematical signature describes fractal behavior.[4]

The importance of fractals to the biologic sciences is becoming increasingly understood. West *et al.*[18,19] have demonstrated that the ubiquitous one-fourth power scaling laws for metabolic rate, heart rate, cardiac output, and biologic structures can be accounted for by the underlying fractal distribution system. These authors have shown that one-fourth power scaling laws define life over as many as 21 orders of magnitude, from microorganisms to the blue whale—a remarkable independence of scale.

Body organs that display oscillating behavior, such as the beating heart, breathing by the lungs, and blood pressure fluctuations, have fractal characteristics as well. These fractal time sequences can be mathematically modeled in the same way as structural fractals. An independence of scale is seen here with "time layered on time": modulation in time sequences evident over short and long periods. Understanding the importance of fractal time for organism health takes the structural fractal toward their functional correlates. Increasing pathology in organ function is evident as fractal timing is lost.[5,6] Goldberger has documented the relationship between normal sinus rhythm and cardiac health. Specific to the lungs, fractal blood flow and ventilation have been identified.[20] Lung units open in an all-or-none behavior called *avalanches*.[21,22] The timing of opening of alveoli and change in airway impedance show power law behavior.

Suki *et al.*[13] have modeled variability seen with VV as a form of noise and have shown that in the face of atelectasis, a noisy PIP can better recruit collapsed lung units and thereby improve Pa_{O_2}. The increase in recruited volume seen with large breaths more than offsets the loss of volume with small breaths. With VV, PIP has been consistently shown to be lower at the same minute ventilation, and therefore, the net increase in P_{aw} that would occur with the addition of volume recruitment maneuvers such as sighs does not occur with VV. Sighs even at the same frequency as the large breaths in VV did not result in sustained improvement in oxygenation.[9] Addition of a suprathreshold noisy signal can increase information transfer in a massively parallel array with all-or-none output.[23] The more massive the parallel array is, the more advantageous the additional noise is. The all-or-none opening of a massively parallel array of alveoli is adaptable to such a model. We can hypothesize that a fractal signal is optimal because such a signal has a greater probability for rare events over a Gaussian signal, meaning a greater likelihood of both large and small signals.[22] As well, these are the characteristics of the signals seen for healthy breathing patterns. Therefore, the fundamental advance of VV over conventional CV is

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using biologic noise to advantage. In this regard, VV has been shown to have both prophylactic and therapeutic advantages.[10,11] From this clinical trial, it is not clear how important the fractal nature of the ventilator output signal is. It is possible that "scrambling" the output file to produce a random rather than a fractal output sequence could result in the same improvement in pulmonary function.

As mentioned, the file used to program RR and V_T in the VV group was data obtained from an awake, spontaneously breathing, chronically instrumented dog. The one-fourth power scaling laws suggest that human data are not necessary. Scaling dog RR to humans should suffice. The data file contained only 376 breaths before looping to repeat itself. However, it is possible that human respiratory data or a file of greater length may be superior. The VV module was designed to maintain minute ventilation constant from breath to breath. Separate variability in rate and V_T could be superior. However, recent work indicates that rapid low-V_T ventilation is associated with intrinsic positive end-expiratory pressure.[24] Therefore, alveolar patency may be well maintained with the small, rapid breaths seen with VV operating in volume divider mode.

Variable output improves other life-support devices as well. Fractal or variable pulsation for whole body perfusion results in superior cerebral venous oxygenation with cardiopulmonary bypass.[25,26] Fractal delivery of cardioplegia solution preserves diastolic function in the heart after aortic cross clamping.[27] Such findings suggest that a fractal signal may be of fundamental importance for all life-support devices.

In conclusion, this first clinical study designed to examine the efficacy of a variable or fractal output signal in a life-support device indicates that VV improves lung function in patients undergoing abdominal aortic surgery. Evidence from animal experimentation and the results of this clinical study indicate that a clinical trial in patients with more severe pulmonary dysfunction, such as acute respiratory distress syndrome, is warranted. The importance of the fractal nature of variable ventilation should be explored further.

This clinical study evolved from the experimental work of W. Alan C. Mutch, M.D. (Professor, University of Manitoba, Winnipeg, Canada), and Gerald R. Lefevre, M.D. (Assistant Professor, University of Manitoba), codevelopers of biologically variable life support.

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