Biologically variable ventilation prevents deterioration of gas exchange during prolonged anaesthesia


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We have studied the time course of changes in gas exchange and respiratory mechanics using two different modes of ventilation during 7 h of isoflurane anaesthesia in pigs. One group received conventional control mode ventilation (CV). The other group received biologically variable ventilation (BVV) which simulates the breath-to-breath variation in ventilatory frequency (f) that characterizes normal spontaneous ventilation. After baseline measurements with CV, animals were allocated randomly to either CV or BVV (P_{O_2} 1.0 with 1.5% end-tidal isoflurane). With BVV, there were 376 changes in f and tidal volume (V_T) over 25.1 min. Ventilation was continued over the next 7 h and blood gases and respiratory mechanics were measured every 60 min. The modulation file used to control the ventilator for BVV used an inverse power law frequency distribution (1/f^a with a=2.3±0.3). After 7 h, at a similar delivered minute ventilation, significantly greater P_{aO_2} (mean 72.3 (SD 4.0) vs 63.5 (6.5) kPa) and respiratory system compliance (1.08 (0.08) vs 0.92 (0.16) ml cm H_2O–1 kg–1) and lower P_{aCO_2} (6.5 (0.7) vs 8.7 (1.5) kPa) and shunt fraction (7.2 (2.7)% vs 12.3 (6.2)% were seen with BVV, with no significant difference in peak airway pressure (16.3 (1.2) vs 15.3 (3.7) cm H_2O). A deterioration in gas exchange and respiratory mechanics was seen with conventional control mode ventilation but not with BVV in this experimental model of prolonged anaesthesia.

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Impaired gas exchange and respiratory mechanics are well known consequences of anaesthesia. Up to 90% of patients show deterioration in arterial oxygenation, increased shunt fraction and decreased respiratory system compliance during anaesthesia, which increases over time. Bendixen, Hedley-Whyte and Laver first proposed that atelectasis contributes to this phenomenon. Using computed tomography, Hedenstierna and colleagues showed that impaired gas exchange during anaesthesia was associated with atelectasis in dependent lung areas.

Recent work has shown that an ‘alveolar recruitment strategy’ can improve arterial oxygenation during general anaesthesia. By combining increasing levels of PEEP up to 15 cm H_2O and tidal volumes up to 18 ml kg–1, they demonstrated improved arterial oxygenation after 40 min of anaesthesia. However, others have shown that PEEP may worsen gas exchange during anaesthesia. Alternative approaches, such as intermittent ‘sighs’ to prevent deterioration in gas exchange during anaesthesia, have been largely unsuccessful.

Although an alveolar recruitment strategy improved gas exchange during general anaesthesia, peak airway pressures were high (up to 40 cm H_2O). A technique to prevent atelectasis without increasing airway pressure would benefit patients requiring prolonged mechanical ventilation during anaesthesia. We have developed a new mode of mechanical ventilation termed biologically variable ventilation (BVV). This computer-controlled ventilator simulates breath-to-breath variation in ventilatory frequency (f) that characterizes normal spontaneous ventilation. In this experiment, changes in f resulted in reciprocal changes in tidal volume (V_T)—low f associated with large V_T and vice versa. Using BVV, we found improved gas exchange at similar mean airway pressures (P_{aw}) and minute ventilation compared with conventional control mode ventilation (CV) in pigs with experimental acute respiratory distress syndrome (ARDS). Improved gas exchange may be caused by the variations in end-inspiratory pressure from the variable V_T. Such pressure variation may enhance the markedly non-linear recruitment of atelectatic regions seen in ARDS.
We postulated that BVV may also prevent the deterioration in gas exchange that occurs during prolonged anaesthesia with monotonous ventilation. We also felt that BVV would improve gas exchange without the increases in airway pressure seen with other volume recruitment strategies. In this experiment, we compared gas exchange and respiratory mechanics in pigs who underwent ventilation with either BVV or CV during prolonged isoflurane anaesthesia.

Materials and methods

This study was approved by the Committee for Animal Experimentation at the University of Manitoba. The recommendations of the Canadian Council on Animal Care were followed. We planned to study 20 pigs, weighing 20–30 kg, allocated to receive one of the two modes of ventilation using blocked randomization (n=2×10). All pigs received atropine 0.6 mg i.m. and ketamine 10 mg kg\(^{-1}\) i.m. for sedation, and isoflurane in oxygen was administered by face mask. While lying supine, the trachea was intubated with a 6.0-mm tracheal tube. Mechanical ventilation with 100% oxygen was started using an Ohio 7000 anaesthesia ventilator at 15 bpm with minute ventilation adjusted to deliver a measured \(V_T\) of approximately 10 ml kg\(^{-1}\). End-tidal isoflurane 2.0% was administered during surgical preparation. Lactated Ringer’s solution 500 ml was administered i.v. by the end of surgery and then infused at 10 ml kg\(^{-1}\) h\(^{-1}\) during the experiment. Pancuronium was administered i.v. for neuromuscular block (20 mg at the outset and 10 mg hourly by infusion). Temperature was maintained at 37±1°C by heating pad and radiant heater.

A double-lumen catheter was inserted into the femoral artery for intermittent blood sampling and continuous recording of arterial pressure. A 7.5-French gauge catheter was inserted into the femoral vein and advanced into the right atrium to measure central venous pressure (CVP). A 7.5-French gauge pulmonary artery catheter was inserted via the external jugular vein and advanced until a satisfactory pulmonary capillary wedge pressure (PCWP) was obtained. Pressure transducers were zero referenced to mid-chest level.

After preparation, the animal was allowed to stabilize for 30 min and the isoflurane concentration was reduced to 1.5% end-tidal. Baseline haemodynamic and respiratory measurements were obtained. Haemodynamic measurements included mean arterial pressure (MAP), mean pulmonary artery pressure (MPAP), PCWP and CVP. Airway flow was measured using a pneumotachograph (Hans Rudolph Inc., Kansas City, MO, USA) at the proximal end of the tracheal tube. All measurements were recorded continuously on a Gould 2600 oscillograph (Gould Inc., Cleveland, OH, USA) and intermittently by an advanced CODAS (Dataq Instruments Inc., Akron, OH, USA) data acquisition system. Cardiac output was measured intermittently by thermodilution using 5-ml injections of room temperature saline (performed in triplicate and averaged).

Arterial and mixed venous (sampled from the distal end of the pulmonary artery catheter) blood gases were measured using a Radiometer ABL300 blood-gas analyser (Copenhagen, Denmark). Arterial and mixed venous oxygen content, oxygen saturation and haemoglobin concentrations were measured using a Radiometer OSM3 hemoximeter (Copenhagen, Denmark) set for porcine blood. All measurements were obtained in duplicate. Static respiratory system compliance (Crs) was measured over 3–5 breaths by clamping the expiratory limb of the ventilatory circuit at end-inspiration for 0.5–1.0 s to obtain a plateau pressure. Mean values are reported. The \(V_T\) used was that which the animal was receiving at the time. This was done so as not to change the mode of ventilation the animal was receiving.

We calculated pulmonary vascular resistance (PVR), shunt fraction (Qs/Qt), Crs (\(\Delta V/\Delta P\)), mean airway pressure (Paw) and mean peak airway pressure (Ppaw). After these measurements were obtained, a manual forced inspiration was performed (Paw 30 cm H\(_2\)O for 60 s) to give all animals the same lung volume history. Animals were then allocated randomly to one of two ventilatory modes: conventional IPPV with \(f\) fixed at 15 bpm (CV group) or IPPV using a computer-controller with variable \(f\) but with a mean of 15.0 bpm (BVV group). Ventilation continued with either CV or BVV for the duration of the experiment.
Anaesthesia and biologically variable ventilation

Every hour for 7 h, haemodynamic and ventilatory data were obtained as above.

The computer-controller and software for the ventilator have been described previously. In this instance, the modulation file used to control ventilator f and VT was generated from an awake animal and scaled to 15 bpm. Briefly, output to control f was updated every 5 ms and changed according to the modulation data file. With BVV, f varied from 8 to 26 bpm. There were 376 f and VT combinations over 25.1 min before the modulation file repeated itself. With BVV, VT was inversely related to the instantaneous f because the ventilator acted as a volume divider. Delivered minute ventilation was not altered.

The data files of airway pressure and volumes were processed to integrate the area under the pressure–time and flow–time curves to give Paw and volume. Ppaw was also calculated. Lengthy measurement periods were undertaken to accurately assess measured f, VT, Paw and Ppaw because of the variability in f and VT after institution of BVV (>120 breaths measured at 4 and 7 h). At the end of each experiment, the animal was killed with a lethal dose of thiopental.

Data were analysed by repeated measures ANOVA. Data are presented as mean (SD), unless otherwise indicated. P≤0.05 was considered significant for group×time interactions or differences between groups. Least squares means test matrices were generated for post hoc comparisons. Bonferroni’s correction was applied when multiple comparisons were examined within groups. When an interaction between variables was possible, analysis of covariance was performed. Post hoc analysis as above. Single comparisons between groups were performed using the Student’s t test; P≤0.05 was considered significant.

Inverse power law analysis was performed as follows: mean instantaneous f was determined (15.0 bpm), then each instantaneous f was subtracted from mean f; this value was squared and then log transformed. These data were divided into incremental bins of equal size to determine their frequency distribution. The probability of each frequency was determined by Ni/N where Ni=number of observations in a given frequency bin and N=total number of observations. A log transform of the probability distribution was derived. The log probability distribution vs log f variation was plotted. The confidence interval and correlation coefficient were derived by regression analysis.

Fig 2 Blood gas and respiratory mechanics for the two experimental groups (mean (SEM)). A: PaO2 vs time for the two experimental groups. Group×time interaction by ANOVA; P<0.0001. With BVV, PaO2 was significantly higher at the end of the study. B: PaCO2 vs time for the two groups. Group×time interaction; P<0.0001. With BVV, PaCO2 was significantly lower. C: Shunt fraction (Qs/Qt) vs time. Group×time interaction; P<0.0001. With BVV, shunt fraction was significantly less. D: Static respiratory system compliance (Crs) vs time. Group×time interaction; P<0.0001. With BVV, Crs remained essentially unchanged during the course of the experiment and was significantly decreased with CV. E: Mean airway pressure (Paw) vs time. Group×time interaction; P=0.528. F: Measured tidal volume (VT) vs time. Group×time interaction; P=0.0005. With BVV, measured tidal volume was greater at 4 and 7 h at similar delivered minute ventilation.
Table 1 Haemodynamic data for the two groups (mean (SD)) (n = 8 in each group). MAP = mean arterial pressure; MPAP = mean pulmonary arterial pressure; PCWP = pulmonary capillary wedge pressure; CVP = central venous pressure; CO = cardiac output; and PVR = pulmonary vascular resistance. *P<0.05 within groups compared with baseline; †P<0.05 between groups

<table>
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<th></th>
<th>Baseline</th>
<th>1 h</th>
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<td>BVV</td>
<td>79.3 (12.5)</td>
<td>81.9 ± 7.5</td>
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<td>77.3 ± 21</td>
<td>71.9 ± 13.9*</td>
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<tr>
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<td>3.3 (2.0)</td>
<td>3.0 ± 1.0</td>
<td>3.3 ± 1.4</td>
<td>3.1 ± 1.1</td>
<td>3.2 ± 1.5</td>
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<td>CV</td>
<td>2.7 (1.2)</td>
<td>2.5 ± 0.4</td>
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<td>2.6 ± 0.6</td>
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Results

We undertook 20 experiments. Three were discarded because of technical problems and one because of suspected hyperthermia. Data were analysed on 16 completed experiments (n = 8 in each group).

With BVV, measured mean f was 14.9 (0.2) bpm. A representative recording of changes in f in one experiment is shown in Figure 1A. Mean Vt was 330 (31) ml. Minimal measured Vt was 197 (43) ml and maximal measured Vt was 676 (120) ml, a mean range of 479 ml. A representative recording of the simultaneous changes in Vt with changes in f is shown in Figure 1B. With BVV, mean Paw was 16.3 (1.3) cm H₂O. Mean minimal Paw (at the lowest mean Vt) was 12.8 (2.1) cm H₂O. Mean maximal Paw (at the highest mean Vt) was 25.9 (4.3) cm H₂O.

Haemodynamic data are shown in Table 1. MAP and MPAP were stable, with only small differences within groups over the course of the experiments. There was a significant group×time interaction for PCWP (P=0.043). At baseline, there was a mean difference of 1.1 mm Hg with the greater pressure with CV. At the end of the study, the mean difference was 0.3 mm Hg and this was not significant. In contrast, there was no significant difference in CVP between groups (group×time interaction; P=0.698). At 6 and 7 h, cardiac output was higher in the CV group. Associated with the differences in cardiac output, mixed venous oxygen tension (PvO₂) was greater in the CV group at 6 and 7 h. There were no differences in PVR between groups.

PvO₂ was similar in the two groups at baseline. By 6 h, PVpO₂ was significantly greater with BVV (Fig. 2A; group×time interaction; P<0.0001). PVpCO₂ was similar at baseline (Fig. 2B). At the end of the study, mean PVpCO₂ was 2.0 kPa greater with CV (group×time interaction; P<0.0001). With BVV, shunt fraction was stable over the course of the experiment. In contrast, shunt fraction increased significantly to 160% of baseline at 7 h with CV (group×time interaction; P<0.0001; Fig. 2C). Because shunt fraction, cardiac output and PVpO₂ are related, analysis of covariance was used to compare shunt fraction to correct for differences in cardiac output and PVpO₂ at the later times between groups. Correcting for differences in cardiac output and PVpO₂ at the later times, shunt fractions remained significantly lower with BVV.

There was a significantly smaller respiratory system compliance (Fig. 2D) with CV by 4 h (group×time interaction; P<0.0001) that persisted for the rest of the experiment. Compliance differed by 19% between groups at the end of the study. There was no group×time interaction for Paw at 4 or 7 h (Fig. 2E; P=0.528).

Table 2 shows minute ventilation data. At baseline, delivered minute ventilation (measured from the back of
At baseline, measured respiratory variation contributes to the deterioration in gas exchange and respiratory mechanics during anaesthesia. During prolonged anaesthesia in pigs, we have shown that BVV resulted in better arterial oxygenation, carbon dioxide clearance and compliance, while shunt fraction was lower compared with CV. Such improvements occurred without BVV being a true facsimile of spontaneous breathing. In this study, changes in $f$ resulted in reciprocal changes in $V_T$ as the ventilator functioned as a volume divider. Independent variation in $V_T$, although possible with the modified ventilator developed, was not attempted. Incorporating such variability could result in a truer modelling of natural breathing.

At baseline, with both groups undergoing ventilation at a similar minute ventilation in standard control mode, there were no differences for any of the measured variables defining gas exchange or respiratory mechanics. The modulation file used to control BVV output was scaled to provide the same mean $f$ as in the control group. Thus adding variation in $f$ and reciprocal variation in $V_T$ at unaltered delivered minute ventilation was the only intervention undertaken. Despite identical starting conditions, measured $V_{T/kg}$ increased with BVV over time while it decreased with CV. A decrease in measured $V_T$ would be expected with CV during prolonged anaesthesia as compliance decreases. This is especially so with anaesthesia circuits where the circle system and tubing are relatively compliant (approximately 2 ml cm$H_2O^{-1}$ litre$^{-1}$ in our system). With BVV, a greater fraction of delivered $V_T$ was used (an increase of 0.9 ml kg$^{-1}$ from baseline; 5% of the 17.7 ml kg$^{-1}$ available). With CV, less of the delivered $V_T$ entered the lungs (a 3% decline from baseline). The difference in compliance between groups at 7 h (19%) can account for the differences in $V_T$. Given the stable gas exchange and respiratory mechanics with BVV, the additional measured $V_T$ appears favourably distributed, implying superior $V_A/Q$ matching. For instance, by the end of the experiment, mean $P_{aCO_2}$ was 2.0 kPa greater with CV. This increase in $P_{aCO_2}$ probably represents an increase in deadspace ventilation with CV over time, given the stable depth of anaesthesia and stable temperature (that is stable metabolism in both groups). At 7 h there was no difference in oxygen consumption between groups (142 (38) ml min$^{-1}$ with CV and 141 (11) ml min$^{-1}$ with BVV), as measured by the Fick equation. However, the statistical power of this finding was low and small changes may have been undetected.

The small differences in $V_T$ cannot account solely for the differences in gas exchange. Almost doubling mean $V_T$ resulted in only small improvements in gas exchange during mechanical ventilation. Thus the manner in which breaths are delivered appears to be important; increasing $V_T$ in a monotonous manner seems to be ineffectual. Deterioration in pulmonary function with CV in our experiment is consistent with the well documented changes during prolonged mechanical ventilation under anaesthesia.

In a model of ARDS, we found 12% greater $V_T$ after 4 h with BVV, with a significant difference in compliance.
between BVV and CV. In our current experiment, in healthy lungs, compliance remained stable in the BVV group. Failure to show an increase may relate to the way compliance was measured in this experiment (3–5 measurements of static compliance during variable breathing so as not to alter the mode of ventilation). In contrast, there was a significant decrease in compliance in the CV group.

Examination of Figure 1B shows the variation in VT over time in one experiment. In this example, mean VT was 334 (63) ml for 239 consecutive breaths over 16.2 min. There was only one breath that exceeded mean VT by 100% (706 ml) which could be defined as a sigh. The ability of sighs to prevent deterioration in gas exchange during prolonged anaesthesia remains controversial. The important difference between BVV and sighs is that BVV does not affect mean pressure over time because both large and small VT are delivered. Frequently delivered sighs of volume ≥100% of mean VT would result in increased Paw and Ppaw over time.

We have not shown that BVV prevents atelectasis. However, shunt fraction correlated with atelectasis, as measured by computed tomography, during anaesthesia (shunt = 1.6 × atelectatic area + 1.7)14. If such results apply to this experiment, then atelectasis in animals undergoing ventilation with BVV would not change (+0.1% atelectatic area) compared with an increase of 2.9% atelectatic area with CV.

Based on analysis of our work, Suki and colleagues proposed a theoretical model of how BVV with its noisy or variable Ppaw could better recruit atelectatic lung.11 The improved gas exchange with BVV could result from stochastic resonance, that is the use of a noisy input (variable end-inspiratory pressure) to enhance output (PaO2) in a non-linear system.15 In our study of severe ARDS, variable ventilation was needed for 1.5–2 h to see improved gas exchange. In this experiment in healthy lungs, advantages were clearly noticeable after only 5 h.

The variation we programmed into our respiratory control files (based on awake or lightly anaesthetized animal breathing patterns) had the characteristics of an inverse power law frequency distribution (1/fα).16 17 Such inverse power law behaviour is ubiquitous in biological rhythms.18 19 Frey and colleagues found that the spontaneous breathing patterns of infants follow such power law distributions20 and suggested that the tonic neural inputs to the respiratory oscillator are noisy. Conventional control mode ventilation (the standard for anaesthesia) eliminates such ‘normal’ noisy ventilatory patterns (Fig. 3). It is not clear if the variability file chosen for BVV in this experiment was optimal. We have successfully used variations with α = 1.5–2.5. Frey and colleagues found that α = 3.2 in term infants.20 A greater a-value is associated with a smaller probability of large variations in f. Airway impedance in humans varies with α = 1.5–2.5.21 Suki and colleagues showed that the incremental avalanche-like recruitment of lung volume, the timing of such recruitment and the changes in airway impedance with such recruitment followed inverse power law behaviour with negative slopes from 1.1 to 2.5.22 23 Inverse power law behaviour can define many features of pulmonary mechanics and gas exchange, and the noise programmed in this experiment appears to be within the range of ‘noise’ seen with other respiratory variables. Importantly, the respiratory variation used with BVV is not random (1/fα with α = 0 or white noise).

Simulation of another physiological phenomenon, respiratory sinus arrhythmia, the normal changes in spontaneous heart rate with the phases of respiration, improves pulmonary gas exchange and circulatory efficiency.24 In anaesthetized dogs, respiratory sinus arrhythmia induced by pacing the diaphragm and concurrently stimulating the vagus nerve during expiration improved shunt fractions and decreased deadspace ventilation compared with constant stimulation or vagal stimulation during inspiration. Respiratory and heart rates can become phase locked which can increase the effects of respiratory sinus arrhythmia.25 26 BVV, by returning normal variation in ventilatory frequency, has resulted in some of the improvements in pulmonary gas exchange described in the experiment by Hayano and colleagues.24

Further refinements in breathing variation are possible with independent control of f and VT, an obvious choice to start to more closely mimic normal breathing.

The better gas exchange and pulmonary mechanics with BVV in this study were similar to results obtained in our studies of ARDS. Those studies showed a therapeutic benefit of BVV. This study suggests a prophylactic benefit and indicates that BVV may be a superior mode for controlled ventilation during anaesthesia. Whether this is the case clinically must await further study.

Acknowledgements

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References

Anaesthesia and biologically variable ventilation


