Optimization of lung ventilation and perfusion in anesthetized horses using a ventilation mode with flow-limited expiration

Joaquin Araos, DVM, PhD, DACVAA; Bernd Driessen, DVM, PhD, DECVP, DACVAA; Jerrianne Brandly, DVM; Emma Gorenberg, VMD, DACVIM; Paul Heerdt, MD, PhD; Alejandro Bruhn, MD, PhD; Manuel Martin-Flores, DVM, DACVAA; Andy Adler, PhD; Klaus Hopster, DVM, PhD, DECVAA*

1Department of Clinical Sciences, College of Veterinary Medicine, Cornell University, Ithaca, NY
2Department of Clinical Studies, School of Veterinary Medicine, University of Pennsylvania, Kennett Square, PA
3Department of Anesthesiology, Yale School of Medicine, New Haven, CT
4Department of Intensive Medicine, School of Medicine, Pontificia Universidad Católica de Chile, Santiago, Chile
5Systems and Computer Engineering, Carleton University, Ottawa, ON, Canada

*Corresponding author: Dr. Hopster (khopster@vet.upenn.edu)

OBJECTIVE
To investigate the mechanisms underlying the improved arterial oxygenation described with flow-limited expiration (FLEX) ventilation in anesthetized horses.

ANIMALS
5 healthy adult research horses.

METHODS
Horses underwent volume-controlled ventilation for 60 minutes (VCV1), followed by 60 minutes of FLEX, and 30 minutes of VCV (VCV2). Main outcomes included the arterial partial pressure of oxygen-to-FIO2 (PF) ratio and electrical impedance tomography (EIT)-derived functional indices at the end of each phase. The EIT data were used to create regional maps of relative lung ventilation and perfusion as well as regional maps of ventilation/perfusion (V/Q) ratios. Ventilation indices derived from EIT included the fraction of expired volume in 1 second (FEV1; %) and the time it took for the EI signal to drop to 50% of the peak signal at end-inspiration (TClose; seconds). Data were analyzed with 2-way ANOVA for repeated measures. P < .05 was considered significant.

RESULTS
The PF ratio increased significantly with FLEX compared to both VCV1 and VCV2 (P < .01). There were no differences in the relative distribution of ventilation nor perfusion between ventilation strategies. However, when ventilation and perfusion were superimposed and V/Q ratio maps were constructed, FLEX had a homogenizing effect toward values of 1.0. The FEV1 was shorter (P < .01) and the TClose was longer (P < .001) in all regions during FLEX compared to both VCV1 and VCV2.

CLINICAL RELEVANCE
Our findings suggest that FLEX ventilation in anesthetized horses enhances regional V/Q matching, likely by prolonging expiratory aeration and reducing airway closure.

Keywords: equine, electrical impedance tomography, anesthesia, oxygenation, perfusion

General anesthesia in horses carries a significantly higher risk for adverse events than in other domestic species.1,2 Lung compression, particularly in dorsocaudal regions of the lungs, is common during dorsal recumbency and leads to expiratory airway closure and atelectasis formation.3-5 Impaired pulmonary gas exchange is a common pathological finding in anesthetized horses, and it has been associated with worse outcomes.6 Optimizing ventilation and gas exchange is therefore a clinical challenge in this species.

Flow-limited expiration (FLEX) ventilation is a novel mode of mechanical ventilation with promising potential to tackle some of these challenges.7-9 In traditional volume-controlled ventilation (VCV),
expiration is directed solely by the passive recoil forces of the respiratory system, producing an exponential expiratory flow pattern with initially high expiratory peak flow rates and rapid lung deflation. Simultaneously, airway pressure drops quickly during passive expiration and the small airways and alveoli in the lungs stay at the set end-expiratory pressure level until the next inspiration cycle starts, which promotes airway closure and atelectasis formation. By contrast, the FLEX mode of ventilation introduces a linear expiratory flow pattern by decelerating the initial expiratory flow in favor of a moderate flow persisting throughout nearly the entire expiration phase. These differences in air flow and airway pressure patterns between VCV and FLEX ventilation are shown (Figure 1). By adopting a linear flow pattern, FLEX ventilation optimizes lung gas exchange function by sustaining a continuous airflow and positive pressure in airways and lungs throughout most of the expiration phase, thereby reducing the extent of alveolar collapse and thus potentially enhancing gas exchange and mitigating the negative effects associated with extended periods of zero flow.

When FLEX ventilation was applied to human patients, it led to significant improvements in the distribution of regional ventilation without affecting hemodynamics. The findings of that study indicated that FLEX ventilation improves the distribution of inspired ventilation as a consequence of more homogeneous lung emptying during expiration. Previous studies in horses have shown significant improvements in arterial blood oxygenation and cardiac output (CO) with FLEX compared to VCV. The exact mechanism by which FLEX results in such a dramatic improvement in oxygenation in anesthetized horses, however, remains unknown.

The present study aimed to describe the mechanisms by which FLEX improves pulmonary oxygen (O₂) uptake. With the use of electrical impedance tomography (EIT), we studied 5 dorsally recumbent anesthetized adult horses and determined functional EIT indices of regional ventilation and perfusion during VCV and FLEX ventilation. The primary outcomes of the study were the effects of FLEX on arterial oxygenation and EIT-derived indices of ventilation and perfusion. Secondary outcomes included differences in systemic and pulmonary hemodynamics and respiratory system mechanics. We hypothesized that FLEX ventilation, by maintaining airflow and hence extending lung aeration throughout the expiratory phase, leads to improved matching of ventilation and perfusion (V/Q matching), which in turn improves pulmonary capillary O₂ uptake and consequently systemic arterial oxygenation.

**Materials and Methods**

This prospective, experimental study was approved by the Institutional Animal Care and Use Committee of the University of Pennsylvania (protocol no. 806775-aacgbc). An a priori statistical power analysis (type II error = 0.2; type I error = 0.05) revealed that a total of 5 horses would be necessary to detect clinically significant differences in arterial partial pressure of O₂ (Pao₂) assuming a clinically relevant difference in Pao₂ of 100 mm Hg with an SD of 15%. Five healthy, university-owned horses were included in this prospective study. Horses (3 geldings and 2 mares) were deemed healthy based on preanesthetic physical examination, had a mean ± SD body weight of 503 ± 89 kg, and were between 3 and 14 years old. They were kept in stalls for 72 hours before anesthesia and fed hay. Food, but not water, was withheld 6 hours before experimentation.

**Anesthesia**

Before anesthesia, the skin over both jugular veins was clipped and aseptically prepared for catheter insertion. 

![Figure 1](https://example.com/figure1.png)  
*Figure 1*—Flow and airway pressure patterns during volume-controlled ventilation and flow-limited expiration ventilation in a representative horse. During flow-limited expiration ventilation, the ventilator was set to let the tidal volume expire over 98% of the set expiratory time.
placement. After infiltration of the skin with lidocaine, a 12-gauge catheter (DayCath; MILA International, Inc) was placed in the left jugular vein and an 8-Fr catheter introducer (Exacta; percutaneous sheath introducer) was placed in the right jugular vein to facilitate placement of a balloon-tipped catheter. A Swan-Ganz standard thermodilution pulmonary artery catheter (Criticath; 7 Fr/110 cm) was placed in the pulmonary artery. Correct placement was confirmed by visual inspection of the pressure waveforms. Cardiac output measurements were not performed due to a technical problem with the monitor at the time of the study. Continuous monitoring of the mean pulmonary artery pressure (mPAP) and mean arterial pressures (MAP) allowed determination of the MAP/mPAP ratio, a robust estimator of the severity of pulmonary artery hypertension, which can develop during extensive small-airway closure and atelectasis.11

Horses were premedicated with 0.5 mg/kg xylazine, IV (100 mg/ml rompun; Bayer Healthcare, LLC) and induced with 0.05 mg/kg midazolam, IV (50 mg/10 mL midazolam HCL; West-Ward, Inc) and 2.2 mg/kg ketamine, IV (zetamine injection; MWI/VetOne). Following induction of anesthesia, horses were orotracheally intubated with a cuffed endotracheal tube (internal diameter, 24 mm) and subsequently positioned in dorsal recumbency on a padded surgical table. Anesthesia was maintained with isoflurane in O2 (inspired concentration of O2 (FIO2) concentration targeted at 1.4 vol% to 1.5 vol% and an end-tidal isoflurane concentration set > 0.9, as this is commonly used in equine anesthesia. Intravenous crystalloid (Vetivex Veterinary pHyLyt injection; Dechra Pharmaceuticals, PLC) solution was administered at a rate of 5 mL/kg/h. A 20-gauge catheter was placed in the facial artery for invasive blood pressure monitoring and arterial blood sampling. The arterial and pulmonary artery catheters were connected to calibrated pressure transducers via rigid extension lines filled with heparinized saline and zeroed to atmospheric pressure at the level of the point of the shoulder.

A 32-electrode, custom-made thoracic belt (analysyti.ca, ON, Canada) was secured vertically around the thorax for EIT measurements immediately before induction of anesthesia and connected to an EIT device (Pioneer Set; Sentec). The hair coat around the point of the shoulder was shaved and zero-end expiratory pressure was programmed. After an equilibration and instrumentation period of approximately 30 minutes. Horses were initially ventilated using VCV for 60 minutes (VCV1) before the ventilation mode was switched to FLEX for 60 minutes. After this period, ventilation was changed back to VCV for another 30 minutes (VCV2). During FLEX ventilation, the only parameter that was changed was the linearization of the expired Vt. During the entire experiment, the mean arterial pressure (MAP), mean pulmonary arterial pressure (mPAP), and arterial blood gases were measured and recorded in 30-minute intervals. Dobutamine (Hospira) was started at 1 μg/kg/min and increased if needed to maintain MAP at a minimum of 70 mm Hg.12 Arterial blood was sampled anaerobically and immediately analyzed (Opti CCA-TS2, Blood Gas Analyzer; Opti Medical Systems). The FiO2 was set > 0.9 and was recorded at the same time. The ratio of PAO2 and FiO2 (PF) ratio was determined as an index of the efficacy of pulmonary O2 gas exchange.13

Respiratory system mechanics

Peak airway pressure and airflow were recorded using a dedicated flow-partitioning device placed between the Y-piece and the endotracheal tube as previously described.14 A pressure differential flow sensor was attached to one limb of the flow partitioning device and connected to a spirometer (NM3 monitor; Respironics). The Vt was obtained by numerical integration of the flow signal. Respiratory data were displayed and collected for further analysis on a personal computer at a sampling rate of 200 Hz (ICU Lab; KleisTEK Engineering). Peak airway pressure end Vt was used to calculate the dynamic compliance of the respiratory system (Crs).

As a measure of intratidal lung overdistension or intratidal recruitment during VCV and FLEX, the stress index (SI) was calculated.15 By analyzing the shape of the pressure-time curve during constant airflow (Supplementary Figure S1), the SI can indicate tidal overdistension when displaying an upward concavity, tidal recruitment when displaying a downward concavity, and normal lung inflation when the shape follows a straight line.

The stress index (SI) was estimated using a validated approach based on the Levenberg-Marquardt method.16 Briefly, during constant flow inflation, the dynamic pressure-time curve can be described by a power equation:

\[
\text{Paw}(t) = a \times t^b + c,
\]

where t is time and a, b, and c are constant coefficients. The coefficient b (SI) is a dimensionless
number that describes the shape of the pressure-time curve. When \( b < 1 \), the pressure-time curve presents a downward concavity, indicating that elastance decreases with time during the breath. When \( b > 1 \), the pressure-time curve presents an upward concavity, indicating that elastance increases with time. When \( b = 1 \), the pressure-time curve is straight, indicating that elastance is constant over time.

### Electrical impedance tomography

Data were acquired continuously at 47 frames/s at 30 and 60 minutes during VCV 1 and FLEX and at 30 minutes during VCV 2. Data were then low-pass filtered using a Butterworth filter with a cut-off frequency of 8 Hz (ventilation analysis) or 0.25 Hz (perfusion analysis). The EIT images were reconstructed using the GREIT algorithm\(^{17} \) applying a forward model based on a horse-shaped finite element model, with segmented regions for the left and right dorsal and ventral lungs.

Ventilation images were generated from a 30- to 120-second recording of uninterrupted ventilation. In each recording, all breaths were identified by locating the time point of end-inspiration in the global EIT signal. The correlation between each breath and the average breath was calculated. Breaths with \( r > 0.98 \) were selected, and then the ensemble was averaged together to create a single, average representative breath of ventilation over the entire recording. For all parameters, the EIT reference was chosen to be the end-expiratory point in the ensemble-averaged data.

Using these averaged reconstructed images, the waveform for each pixel in each averaged recording was analyzed to calculate the following parameters:

- Fraction of expired volume in 1 second (FEV 1%; %): the percent fraction of EIT ventilation signal after 1 second of expiration compared to the signal at end-inspiration.
- \( T_{CO2}50 \) (seconds): the time it took for the EIT ventilation signal to drop to 50% of the peak signal at end-inspiration.
- \( \Delta EELI_{VCV-FLEX} \): the change in global end-expiratory lung impedance (EELI; a surrogate of end-expiratory lung volume) between the end-expiration point during FLEX and its value during VCV during the first part of the study and during VCV and FLEX in the last part of the study was calculated.\(^{12} \)

Perfusion images were generated from data acquired during an end-expiratory pause. A bolus of 120 mL of hypertonic saline 7.2% was given rapidly through the jugular catheter while recording EIT data at the same rate as during ventilation.\(^{18} \) From these waveforms, the deviation between preinjection and each time point was calculated. The instant of maximal contrast in the global signal from the saline bolus in the lung regions was chosen.\(^{18} \) The perfusion image represents the pixel value of each waveform at the instant of maximum contrast. When employing a bolus technique for measuring lung perfusion, it is essential to ensure that the signal originating from the bolus traveling through the heart is excluded. We manually verified in all animals that the perfusion image contained less than 5% of contribution from the heart.\(^{18} \)

The regional relative (%) ventilation and perfusion impedance changes were used to create regional maps of relative V/Q ratios.\(^{19} \)

### Data analysis

Data were analyzed using the statistical software SAS 9.3 (SAS Institute, Inc) and GraphPad Prism Version 7 (GraphPad Software, Inc). Visual assessment of qq-plots and the Shapiro-Wilk test were used to confirm the normal distribution of model residuals of dependent variables. Outcome variables were compared using 2-way ANOVA for repeated measures with treatment and time treated as categorical variables, followed by Bonferroni correction for multiple comparisons. The level of significance was set to 5% (\( \rho < .05 \)). After initial data analysis, we observed no significant intratreatment differences between T30 and T60 measurements, both during VCV 1 and FLEX. Therefore, data are pooled and reported together during VCV 1 and FLEX.

### Results

All horses completed the study. No differences in dobutamine administration were seen as all horses stayed on the initial set dobutamine infusion rate of 1 \( \mu g/kg/min \). The pulmonary gas exchange, hemodynamic, and respiratory mechanics data are shown (Table 1). The PF ratio was higher at all times during

### Table 1—Pulmonary gas exchange, hemodynamic, and respiratory mechanics in 5 dorsally recumbent, anesthetized horses receiving volume-controlled ventilation and flow-limited expiration ventilation.

<table>
<thead>
<tr>
<th></th>
<th>VCV 1</th>
<th>VCV 2</th>
<th>FLEX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paco2 (kPa)</td>
<td>24.8 ± 5.8</td>
<td>62.5 ± 4.9*</td>
<td>39.3 ± 5.3*</td>
</tr>
<tr>
<td>Paco2 (mm Hg)</td>
<td>192 ± 44</td>
<td>462 ± 34</td>
<td>295 ± 40</td>
</tr>
<tr>
<td>PF ratio (kPa)</td>
<td>27.3 ± 6.4</td>
<td>67.8 ± 5.4*</td>
<td>42.4 ± 5.7*</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>211 ± 46</td>
<td>502 ± 37</td>
<td>318 ± 43</td>
</tr>
<tr>
<td>PaCO2 (kPa)</td>
<td>6.1 ± 0.5</td>
<td>6.2 ± 0.5</td>
<td>5.9 ± 0.4</td>
</tr>
<tr>
<td>PaCO2 (mm Hg)</td>
<td>45 ± 5</td>
<td>46 ± 4</td>
<td>44 ± 3</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>85 ± 11</td>
<td>90 ± 9</td>
<td>91 ± 6</td>
</tr>
<tr>
<td>mPAP (mm Hg)</td>
<td>33 ± 2</td>
<td>28 ± 3*</td>
<td>30 ± 6</td>
</tr>
<tr>
<td>mPAP/MAP</td>
<td>2.5 ± 0.2</td>
<td>3.2 ± 0.4*</td>
<td>3.0 ± 0.3*</td>
</tr>
<tr>
<td>Cdyn (ml/cm H2O)</td>
<td>0.9 ± 0.1</td>
<td>1.2 ± 0.1*</td>
<td>1.0 ± 0.1</td>
</tr>
<tr>
<td>Pip (cm H2O)</td>
<td>31 ± 3</td>
<td>28 ± 2</td>
<td>30 ± 4</td>
</tr>
<tr>
<td>SI</td>
<td>0.87 ± 0.11</td>
<td>1.01 ± 0.06*</td>
<td>0.91 ± 0.12*</td>
</tr>
</tbody>
</table>

Cdyn = Dynamic compliance of the respiratory system. FLEX = Flow-limited expiration. Paco2 = Arterial partial pressure of CO2. PaO2 = Arterial partial pressure of O2. PF ratio = Paco2/Pao2 ratio. MAP = Mean arterial pressure. MAP/mPAP = Ratio of MAP to mPAP. mPAP = Mean pulmonary artery pressure. Pip = Peak inspiratory pressure. SI = Stress index. VCV = Volume-controlled ventilation. VCV 1 = 60 minutes of VCV. VCV 2 = 30 minutes of VCV following VCV 1 and 60 minutes of FLEX.

* \( P < .05 \) VCV 1 vs VCV 2. ** \( P < .05 \) VCV 2 vs FLEX. *** \( P < .05 \) VCV 2 vs FVC 1.
FLEX compared to VCV1 and VCV2. The PF ratio was higher during VCV2 compared to VCV1. The mode of ventilation (VCV vs FLEX) did not have any impact on the measured arterial partial pressure of CO2 (PacO2) or the MAP. The mPAP, however, decreased significantly with FLEX compared to VCV1. The MAP/mPAP ratio was higher during FLEX compared to VCV1 and VCV2. During VCV, the MAP/mPAP was higher than during VCV1. During FLEX, the C02 was higher than during VCV1. The SI increased with FLEX compared to VCV1 and VCV2.

Data derived from EIT analysis are shown (Table 2). There were no differences in absolute or relative distribution or magnitude of aeration between ventilation modes during inspiration. A representative regional impedance change during VCV and FLEX is shown (Figure 2). The FEV1 was significantly shorter, while the TClose50 was significantly longer during FLEX compared to VCV1 and VCV2 in all evaluated lung regions. A representative map of FEV1 in a horse is displayed. The different pattern of expiration between VCV and FLEX is shown (Supplementary Video S1).

The EELI increased with FLEX (ΔEELI [arbitrary units] from VCV1-FLEX = 426 ± 122 P = .02) and decreased when switching to VCV2 (ΔEELI [arbitrary units] = −203 ± 55, P = .05). An increase in EELI during FLEX in one representative horse is shown (Figure 2). The small functional images indicate the gained EELI during VCV1-FLEX and lost EELI during FLEX-VCV2.

The absolute magnitude of perfusion was higher during FLEX compared to VCV2 in the right dorsal region, higher during FLEX compared to both VCV1 and VCV2 in the right ventricular (RV) region, and higher during FLEX compared to VCV1 and VCV2 in the left dorsal region (Table 2). No differences in relative distribution of perfusion were noted between VCV and FLEX ventilation.

The relative regional distribution of ventilation and perfusion in a horse is shown (Figure 3). The superimposition of regional relative ventilation and perfusion to create maps of relative V/Q ratios is illustrated. FLEX appeared to homogenize the regional distribution of relative V/Q ratios, converging toward a value near 1.0.

<table>
<thead>
<tr>
<th></th>
<th>VCV1</th>
<th>FLEX</th>
<th>VCV2</th>
</tr>
</thead>
<tbody>
<tr>
<td>VtEIT (AU)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RD</td>
<td>3,829 ± 2,471</td>
<td>3,646 ± 2,215</td>
<td>3,904 ± 2,683</td>
</tr>
<tr>
<td>RV</td>
<td>6,084 ± 2,754</td>
<td>5,174 ± 2,285</td>
<td>5,377 ± 2,502</td>
</tr>
<tr>
<td>LD</td>
<td>2,773 ± 1,863</td>
<td>2,997 ± 2,057</td>
<td>2,923 ± 1,808</td>
</tr>
<tr>
<td>LV</td>
<td>3,247 ± 903</td>
<td>2,658 ± 1,084</td>
<td>2,984 ± 850</td>
</tr>
<tr>
<td>VtEIT (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RD</td>
<td>22 ± 10</td>
<td>23 ± 10</td>
<td>23 ± 10</td>
</tr>
<tr>
<td>RV</td>
<td>37 ± 15</td>
<td>35 ± 13</td>
<td>35 ± 13</td>
</tr>
<tr>
<td>LD</td>
<td>19 ± 12</td>
<td>21 ± 12</td>
<td>20 ± 11</td>
</tr>
<tr>
<td>LV</td>
<td>23 ± 14</td>
<td>21 ± 14</td>
<td>22 ± 13</td>
</tr>
<tr>
<td>FEV1 (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RD</td>
<td>81 ± 16</td>
<td>30 ± 8*</td>
<td>79 ± 14*</td>
</tr>
<tr>
<td>RV</td>
<td>64 ± 10</td>
<td>23 ± 2*</td>
<td>61 ± 4*</td>
</tr>
<tr>
<td>LD</td>
<td>66 ± 8</td>
<td>23 ± 9*</td>
<td>65 ± 9*</td>
</tr>
<tr>
<td>LV</td>
<td>53 ± 4</td>
<td>15 ± 1*</td>
<td>50 ± 1*</td>
</tr>
<tr>
<td>TClose50 (seconds)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RD</td>
<td>0.4 ± 0.1</td>
<td>2.2 ± 0.1*</td>
<td>0.6 ± 0.0a</td>
</tr>
<tr>
<td>RV</td>
<td>0.8 ± 0.1</td>
<td>2.7 ± 0.1*</td>
<td>0.8 ± 0.0a</td>
</tr>
<tr>
<td>LD</td>
<td>0.7 ± 0.1</td>
<td>2.4 ± 0.0*</td>
<td>0.7 ± 0.0a</td>
</tr>
<tr>
<td>LV</td>
<td>1.0 ± 0.1</td>
<td>3.2 ± 0.1*</td>
<td>1.0 ± 0.1a</td>
</tr>
<tr>
<td>PerfusionEIT (AU)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RD</td>
<td>788 ± 108</td>
<td>1,118 ± 159</td>
<td>704 ± 235a</td>
</tr>
<tr>
<td>RV</td>
<td>891 ± 193</td>
<td>1,503 ± 256*</td>
<td>829 ± 162a</td>
</tr>
<tr>
<td>LD</td>
<td>840 ± 173</td>
<td>1,134 ± 112</td>
<td>903 ± 154</td>
</tr>
<tr>
<td>LV</td>
<td>507 ± 65</td>
<td>931 ± 75*</td>
<td>570 ± 11a</td>
</tr>
<tr>
<td>PerfusionEIT (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RD</td>
<td>26 ± 1</td>
<td>24 ± 6</td>
<td>23 ± 3</td>
</tr>
<tr>
<td>RV</td>
<td>29 ± 9</td>
<td>32 ± 1</td>
<td>28 ± 113</td>
</tr>
<tr>
<td>LD</td>
<td>28 ± 8</td>
<td>24 ± 5</td>
<td>30 ± 10</td>
</tr>
<tr>
<td>LV</td>
<td>17 ± 2</td>
<td>20 ± 12</td>
<td>19 ± 5</td>
</tr>
</tbody>
</table>

Electrical impedance tomography (EIT) data during different modes of ventilation. AU = arbitrary units. FEV1 (%) = Fraction of expired volume in 1 second. LD = Left dorsal lung region. LV = Left ventral lung region. PerfusionEIT (AU) = Absolute change in impedance during end-expiratory pause and bolus injection of hypertonic saline. PerfusionEIT (%) = Change in impedance during end-expiratory pause and bolus injection relative to the total change. RD = Right dorsal lung region. RV = Right ventral lung region. TClose50 (seconds) = Time it took for 50% of tidal volume to be exhaled. VtEIT (AU) = Absolute change in impedance during tidal ventilation. VtEIT (%) = Change in impedance during tidal ventilation relative to the total change.

*P < .05 FLEX vs VCV1. **P < .05 VCV2 vs FLEX.
The data of this study confirm improved pulmonary O2 uptake by FLEX ventilation, as revealed by a significant increase in the PF ratio.7,10 The data also support our hypothesis that by sustaining continuous airflow and positive pressure in the airways and lungs throughout the expiration phase, FLEX ventilation maintains prolonged lung aeration and hence reduces the extent of alveolar collapse.

Our data add to the current body of knowledge by demonstrating a significant regional effect of FLEX ventilation on the expiratory pattern. Both the reduced FEV1 and the prolonged TClose50 clearly indicate that the entire lung stays longer and better aerated during FLEX ventilation. This finding is further supported by the significant increase in EELI, a valid surrogate of end-expiratory lung volume. Increased CRS and SI with FLEX as compared to VCV are further evidence of more effective alveolar recruitment with FLEX ventilation. The striking improvement in oxygenation observed with FLEX ventilation and indicated by the far higher PF ratios measured is likely at least in part due to a reduction in dynamic airway closure during expiration and improvement in V/Q ratios as suggested by the maps of relative V/Q ratios.

As mentioned previously, general anesthesia in horses, particularly when maintained with volatile anesthetics, is associated with a higher incidence of adverse events including markedly impaired oxygenation. Their steep, sloping diaphragm determines that the dorsally recumbent horse will be at risk of dorsocaudal lung compression by the abdominal viscera.4 Up to 40% to 50% of the lung has been shown to be at risk of terminal airway closure or atelectasis formation.20 This leads to abnormal O2 exchange and frequently to hypoxemia, which has been associated with increased complications in equine anesthesia.6

Ventilation using FLEX in this study significantly increased the PF ratio compared to VCV, in line with previous studies7,10 showing improved oxygenation with FLEX ventilation in anesthetized horses. Importantly, in our study transitioning back to VCV after FLEX ventilation resulted in subsequent reductions in the PF ratio, although most parameters did not reverse completely back to VCV1, at least over the 30-minute observation period we had chosen. The FLEX mode differs from standard VCV by linearizing the expiratory flow. Commonly, expiratory flow follows an exponential function, which results in a rapid emptying of alveoli. The rapid rate, at which the lung is deflating during VCV, was evidenced by the calculated parameters FEV1 and TClose50. The FEV1 revealed that within 1 second of expiration during VCV, between 50% and 80% of the Vt had been lost from the lung. Similarly, the TClose50 revealed that it took only 0.5 to 1.0 seconds to deflate the lung by 50% of the Vt. In contrast, during FLEX ventilation only 15% to 30% of the Vt was exhaled within the first second of expiration, while it took 2.1 to 3.2 seconds to deflate the lung by 50% of the Vt. This notable difference in the expiratory dynamics between FLEX ventilation and VCV is further corroborated in

Figure 2—Representative electrical impedance tomography findings in one horse. A—Regional ventilation impedance curves (ΔZ) over time in arbitrary units (AU) during volume-controlled ventilation (VCV) and flow-limited expiration (FLEX) ventilation. Different colors represent the different lung regions. B—Fraction of expired volume in 1-second (FEV1) values for the respective pixels during VCV and FLEX ventilation. Dark blue corresponds to an FEV1 of 0% whereas lighter blue to 1 of 100%. C—Global impedance curve during 60 minutes of VCV (VCV1), FLEX ventilation, and 30 minutes of VSV (VCV2), signifying an increase in end-expiratory lung impedance (EELI) during FLEX ventilation, in 1 representative horse. The small functional images indicate the amount of gained EELI during VCV1-FLEX ventilation (in blue) and the amount lost during FLEX-VCV2 ventilation (in red).

Figure 3—Electrical impedance tomography images of ventilation and perfusion (A) and maps of relative ventilation and perfusion (B). B—Relative distribution maps of ventilation (ZV) and perfusion (ZQ) impedances as a ratio of both values for each region. Ventilation with FLEX seems to have a homogenizing effect on the magnitude of regional relative ventilation/perfusion ratios. LD = Left dorsal lung region. LV = Left ventral lung region. RD = Right dorsal lung region. RV = Right ventral lung region. *P < .05 compared to VCV1.

Discussion

The data of this study confirm improved pulmonary O2 uptake by FLEX ventilation, as revealed by a significant increase in the PF ratio.7,10 The data also support our hypothesis that by sustaining continuous airflow and positive pressure in the airways and lungs throughout the expiration phase, FLEX ventilation maintains prolonged lung aeration and hence reduces the extent of alveolar collapse.

Our data add to the current body of knowledge by demonstrating a significant regional effect of FLEX ventilation on the expiratory pattern. Both the reduced FEV1 and the prolonged TClose50 clearly indicate that the entire lung stays longer and better aerated during FLEX ventilation. This finding is further supported by the significant increase in EELI, a valid surrogate of end-expiratory lung volume. Increased CRS and SI with FLEX as compared to VCV are further evidence of more effective alveolar recruitment with FLEX ventilation. The striking improvement in oxygenation observed with FLEX ventilation and indicated by the far higher PF ratios measured is likely at least in part due to a reduction in dynamic airway closure during expiration and improvement in V/Q ratios as suggested by the maps of relative V/Q ratios.

As mentioned previously, general anesthesia in horses, particularly when maintained with volatile anesthetics, is associated with a higher incidence of adverse events including markedly impaired oxygenation. Their steep, sloping diaphragm determines that the dorsally recumbent horse will be at risk of dorsocaudal lung compression by the abdominal viscera.4 Up to 40% to 50% of the lung has been shown to be at risk of terminal airway closure or atelectasis formation.20 This leads to abnormal O2 exchange and frequently to hypoxemia, which has been associated with increased complications in equine anesthesia.6
Supplementary Video S1. We assume that by prolonging the time the lungs are above end-expiratory lung volume during expiration, FLEX reduces cyclic airway closure and therefore improves regional and global matching of ventilation and perfusion across the duration of the breathing cycle, contributing to improved arterial oxygenation.

The global EELI increased significantly, albeit mildly, when FLEX ventilation was started. End-expiratory lung impedance has been shown to correlate with end-expiratory lung volume and therefore has been used to estimate intraoperative changes in lung volumes. The increase in EELI could represent alveolar recruitment during FLEX ventilation and account, at least in part, for the increase in $C_{rs}$. Another indicator of effective recruitment during FLEX ventilation was the increase in the SI value. Since the SI analyzes the shape of the airway pressure-time curve, it has been used to identify different breath profiles. Values ≤ .95 suggest the presence of tidal recruitment. This is described for lungs that start inspiration at lower end-expiratory lung volumes. As inflation continues and there is a gain in volume, the compliance increases, and therefore the increase in airway pressure per unit time decreases, rendering an airway pressure with a downward convexity (see Supplementary Figure S1). On the other hand, values between 0.95 and 1.05, which represent a linear pressure-time curve, suggest that the lung maintains a constant compliance during tidal inflation. Our results showed that SI increased from a mean of 0.85 during VCV to near 1.0 during FLEX ventilation, suggesting that intratrval recruitment was eliminated during the latter mode of ventilation, providing further evidence of an increase in end-expiratory lung volume maintained with FLEX. Importantly, when switching back to the VCV mode, the EELI and SI values decreased again.

An important pathological feature of anesthesia in horses is a marked increase in pleural pressures, likely a consequence of the compressive effect of abdominal organs over the chest wall. Expiratory pleural pressures higher than 15 cm H$_2$O have been described for the dorsally recumbent horse, resulting in markedly negative transpulmonary pressures and therefore reduced end-expiratory lung volumes. These events are largely responsible for the higher airway pressures developing during ventilation of anesthetized horses compared to other species such as humans. The use of higher airway pressures during mechanical ventilation can impair the cardiovascular system. Further, reductions in the V/Q ratios can result in local alveolar hypoxia and hence trigger pulmonary vasoconstriction. These combined factors can contribute to increased RV afterload resulting in decreased CO and systemic hypotension. Our results showed that absolute lung perfusion at end-expiration increased significantly with FLEX ventilation, suggesting a significant increase in the magnitude and distribution of CO across the pulmonary circulation. This observation is supported by recent data in FLEX-ventilated horses by our group showing a significant increase in CO measured with the pulmonary thermodilution method. This finding, along with a significant reduction in mPAP and a higher MAP/mPAP ratio suggests likely better RV function and hence more favorable conditions for potentially optimizing RV function during FLEX ventilation. Several factors, such as increased EELI, extended aeration during expiration, and improved regional matching of ventilation and perfusion, could all have contributed to these favorable findings during FLEX ventilation. Future studies should confirm these preliminary findings while providing a more comprehensive and direct evaluation of RV function in this setting.

Our study has limitations. First, it is a highly controlled study in nonsurgical horses and with a small sample size. Therefore, its applicability to the general equine surgical population needs to be further evaluated in prospective clinical studies. Also, the order of ventilation modes was not randomized but determined to start with VCV followed by FLEX and ending with VCV. This was done to eliminate possible effects of time and duration under general anesthesia as well as individual differences in pulmonary function between horses. Randomizing these would have resulted in a larger sample size to have a sufficient number of horses. In addition, this fixed ventilation design allowed us to compare our findings to a study published by Borgmann et al using a similar experimental protocol. Further, we did not employ positive end-expiratory pressure (PEEP) with any ventilation strategy. It has been shown that PEEP helps improve overall lung gas exchange efficiency in anesthetized horses. However, a recent study by our group showed that FLEX ventilation with PEEP was superior to VCV with PEEP in related outcomes similar to those reported here. Third, EIT-estimated lung perfusion was only evaluated at end-expiration; therefore, future studies should evaluate how FLEX ventilation impacts end-inspiratory lung perfusion. Finally, we did not directly assess RV function, and future studies should use a combination of direct pressure measurements with echocardiography.

In conclusion, we showed that FLEX ventilation significantly extends regional and global expiratory aeration and increases EELI compared to VCV, contributing to an increased $C_{rs}$ and a drastic improvement in arterial oxygenation. Further, our results suggest improved matching of regional V/Q matching, as well as more favorable conditions for RV function during FLEX. Randomized clinical trials should be conducted to further confirm these findings in larger populations and to evaluate relevant outcomes such as the rate of postoperative complications when compared to traditional ventilation modes.

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References


Supplementary Materials

Supplementary materials are posted online at the journal website: avmajournals.avma.org