

Flow-controlled expiration improves respiratory mechanics, ventilation, and gas exchange in anesthetized horses

Klaus Hopster, DMV, PhD*; Samuel D. Hurcombe, MS; Keith Simpson, MRCVS, MIET; Ashley R. VanderBroek, DVM; Bernd Driessen, DMV, PhD

University of Pennsylvania, School of Veterinary Medicine, New Bolton Center Campus, Kennett Square, PA

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

<https://doi.org/10.2460/ajvr.21.10.0158>

OBJECTIVE

Mechanical ventilation is usually achieved by active lung inflation during inspiration and passive lung emptying during expiration. By contrast, flow-controlled expiration (FLEX) ventilation actively reduces the rate of lung emptying by causing linear gas flow throughout the expiratory phase. Our aim was to evaluate the effects of FLEX on lung compliance and gas exchange in anesthetized horses in dorsal recumbency.

ANIMALS

8 healthy horses.

PROCEDURES

All animals were anesthetized twice and either ventilated beginning with FLEX or conventional volume-controlled ventilation in a randomized, crossover design. Total anesthesia time was 3 hours, with the ventilatory mode being changed after 1.5 hours. During anesthesia, cardiac output (thermodilution), mean arterial blood pressures, central venous pressure, and pulmonary arterial pressure were recorded. Further, peak, plateau, and mean airway pressures and dynamic lung compliance (C_{dyn}) were measured. Arterial blood gases were analyzed every 15 minutes. Data were analyzed using ANOVA ($P < 0.05$).

RESULTS

FLEX ventilation resulted in significantly higher arterial oxygen partial pressures (521 vs 227 mm Hg) and C_{dyn} (564 vs 431 mL/cm H₂O) values compared to volume-controlled ventilation. The peak and plateau airway pressure were lower, but mean airway pressure was significantly higher (4.8 vs 9.2 cm H₂O) in FLEX ventilated horses. No difference for cardiovascular parameters were detected.

CLINICAL RELEVANCE

The results of this study showed a significant improvement of the Pao_2 and C_{dyn} without compromising the cardiovascular system when horses were ventilated by use of FLEX compared to conventional ventilation.

General anesthesia in horses is associated with a high perianesthetic mortality rate.¹ Prolonged procedures and their accompanying anesthetic complications including hypoxemia have been associated with increased risks during the recovery period and increased postoperative complications.^{2,3} The treatment of hypoxemia during general anesthesia could therefore lead to an improvement of the postanesthetic and postoperative outcome in horses. The main reason for hypoxemia during anesthesia is atelectasis, the formation of nonaerated lung areas^{4,5}; the primary mechanism for atelectasis formation in horses is compression atelectasis. When the horse is positioned in dorsal recumbency, the large weight of the abdominal viscera lies directly on the diaphragm leading to compression of the lungs.⁶ The caudodor-

sal lung fields are preferentially perfused by relatively large and stiff pulmonary arteries, which resist the extreme changes in intrathoracic pressure.⁷ The compression of these lung fields results in small airway collapse, but continued preferential perfusion leads to a significant VQ mismatch. This causes right to left pulmonary shunting, measuring as much as 33% of cardiac output (CO).⁸

Several ventilation strategies have been described to recruit lung tissue, improve oxygenation, and reduce intra- and postoperative complications. Multiple studies showed that an initial recruitment maneuver followed by sustained positive end-expiratory pressure (PEEP) can improve gas exchange in anesthetized horses.⁹⁻¹² These authors also showed that high peak airway pressures during inspiration

are necessary to open lungs and keep them open. However, while the effects of various modifications of the inspiratory phase have been investigated,^{10,13-15} with the exception of PEEP,¹⁶ modifications of the expiratory phase have received little attention.

In patients with low pulmonary compliance or high body mass, expiration is relatively rapid compared to that in patients with high compliance or lower body mass.¹⁷ This rapid lung emptying means that fast and slow compartments empty in an inhomogeneous fashion and may result in increased shear stress in the lung parenchyma and higher risks for pulmonary atelectasis. In these patients, flow limitation and air trapping result from caliber reductions of small airways in response to high local flow rates.¹⁸

Flow-controlled expiration (FLEX) ventilation is a new procedure that modulates the otherwise passive expiration phase. By reducing the initial high-expiratory peak flow to a more linear flow, it causes an expiratory gas flow to persist throughout the complete expiratory phase. When FLEX is applied to human patients undergoing neurosurgery, it increases ventilation in the dorsal-dependent lung regions, thereby homogenizing the ventilation distribution without affecting the hemodynamics.¹⁹ The findings of that study indicate that FLEX improves the distribution of inspired ventilation as a consequence of more uniform homogeneous lung emptying during expiration and can be used in adult patients under controlled mechanical ventilation during general anesthesia. Furthermore, to reach comparable PaO_2 -to-inspiratory oxygen concentration ratios, lower PEEP was required with FLEX ventilation than without.²⁰

The aim of this study was to perform this ventilation mode during general anesthesia in dorsally recumbent horses. We hypothesized that the new ventilation mode FLEX would improve respiratory mechanics and gas exchange without altering hemodynamics. Therefore, we investigated respiratory mechanics, oxygenation, and hemodynamics in horses ventilated with and without FLEX.

Materials and Methods

The Tefonius Large Animal Anesthesia Workstation is a large animal anesthesia machine with an integrated piston driven ventilator. For our study, the software of the piston driven ventilator was modified to perform FLEX ventilation. Image editing software (Phase Editor; Vetronics Services Ltd) was used to program the ventilator to release the delivered tidal volume during the expiration phase in a linear fashion. The inspired volume was measured, and the software calculated the flow it would take to exhale it at a constant rate that ends at the time of end-expiration.

After successful modification of the mechanics and a configuration and update of the controlling software, the FLEX-ventilation mode was applied to 2 polyethylene barrels with a volume of 200 L each. Five different tidal volumes (5, 7, 7.5, 8.5, and 10 L) were tested by use of 3 different respiratory rates (3,

5, and 7 breaths/min) each for 3 hours. Ventilation pressures and inspiratory and expiratory volumes were measured to ensure that the software and ventilator were performing as programmed.

Animals

The study was approved by the Institutional Animal Care and Use Committee of the University of Pennsylvania, trial registry No. 806775-aaecgbc. A statistical a priori power analysis (type II error = 0.2; type I error = 0.05) showed that 8 animals are necessary to detect clinically significant changes in PaO_2 and C_{dyn} , assuming a difference in PaO_2 of 100 mm Hg and a difference in C_{dyn} of 100 mL/cm H_2O , with an SD of 15% being clinically relevant.

Eight healthy (based on preanesthetic physical examination) university-owned horses with a mean ($\pm$ SD) body weight of 525 ± 41 kg and a mean age of 8 ± 4 years were used in this crossover prospective study. Horses were kept in stalls 12 to 24 hours prior to each anesthesia and were fed hay. Food, but not water, was withheld 8 hours before experimentation. Horses were randomly assigned to the group first ventilated with FLEX mode and then switched to conventional volume-controlled mechanical ventilation (VCV) after 90 minutes or the group first ventilated with VCV mode and then switched to FLEX (by use of a computer-generated randomization list). Minimum wash-out period between both experiments was 2 weeks.

Instrumentation

Before anesthesia the skin over both jugular veins was clipped and surgically prepared for catheter placement. After infiltration of the skin with lidocaine a 12-gauge catheter was placed into the left jugular vein and two 8F catheter introducers were separately placed in the right jugular vein to facilitate the placement of 2 balloon tipped catheters. A Swan-Ganz standard thermodilution pulmonary artery catheter was placed into the pulmonary artery and a second Swan-Ganz catheter was placed into the right atrium. Correct placement was confirmed by visual inspection of the pressure waveforms.

Anesthesia

All horses were premedicated with 0.8 mg/kg of xylazine IV and induced with 0.05 mg/kg of midazolam and 2.2 mg/kg ketamine IV. Following induction of anesthesia, all horses were intubated with a cuffed murphy tube (internal diameter, 24 mm) and subsequently positioned on a thick foam mattress in dorsal recumbency. Anesthesia was maintained with isoflurane in oxygen. End-tidal isoflurane concentration was targeted at 1.2%. Intravenous crystalloid solution was administered at a rate of 5 mL/kg/h and dobutamine was given at a rate of 0.5 $\mu\text{g/kg/min}$ and adjusted to effect to maintain a mean arterial blood pressure (MAP) above 70 mm Hg during anesthesia. The transverse facial artery was cannulated with a 20-gauge catheter for invasive blood pressure monitoring and arterial blood sampling. The catheter was connected to a calibrated pressure transducer via fluid-filled (heparinized

saline [0.9% NaCl] solution) rigid extension lines and zeroed to atmospheric pressure at the level of the shoulder.

At the end of anesthesia, the horses were sedated with xylazine (0.2 mg/kg) IV and allowed to recover with head-tail-rope assistance. The orotracheal tube was removed and horses were nasotracheally intubated to allow nasal O₂ insufflation for the recovery period (15 L/min).

Ventilation strategy and experimental design

For the present study, an anesthesia workstation operating with an electronically driven piston ventilator was used. Prior to the experiment, the software of the ventilator was modified to allow linear release of a delivered tidal volume (see phase 1).

At intubation, the endotracheal tube was connected to the ventilator and all horses were immediately ventilated with a VCV mode and an inspiratory-to-expiratory ratio of 1:2. Tidal volume was set to 14 mL/kg throughout the experiment, while respiratory rate was adjusted to maintain an end-tidal CO₂ tension of 35 to 40 mm Hg.

All horses were anesthetized twice and were either ventilated using the linear release of the delivered tidal volume (eg, FLEX) for the first 90 minutes followed by conventional VCV for 90 minutes or vice versa (**Supplementary Figure S1**).

Airway pressures as well as the dynamic compliance (C_{dyn}) were measured with a pitot-based flow meter (H-Lite; Morpheus Engineering). The flowmeter was calibrated with a 3-L calibration syringe prior each experiment.

During anesthesia administered every 10 minutes, the MAP, pulmonary arterial pressure (PAP), central venous pressure, and heart rate were measured. The respiratory rate, inspiratory oxygen concentration, peak inspiratory pressure (PIP), plateau airway pressure, mean airway pressure (P_{mean}), and C_{dyn} were recorded every 5 minutes. For the measurement of CO by thermodilution, iced saline solution (1 mL/15 kg) was injected manually through the

catheter into the right atrium at end-expiration. The temperature of the injectate was measured via an inline temperature probe, and the temperature change in the pulmonary artery was analyzed to calculate the CO. Five injections were performed, and the average of the closest 3 CO values was used. Arterial blood (2 mL) was sampled every 15 minutes and analyzed immediately with a blood gas analyzer^m to measure the Pao₂ and the arterial partial pressure of carbon dioxide.

Statistical analysis

Data was analyzed with statistical software (SAS version 9.3; SAS Institute Inc; Prism version 7; GraphPad Software Inc). Visual assessment of qq-plots and the Shapiro-Wilk test was used to confirm normal distribution of model residuals of dependent variables. Variables were compared to baseline and between groups using a 2-factorial variance analysis for repeated measurements and Bonferroni correction for multiple comparisons. The level of significance was set to 5% ($P < 0.05$).

Results

There were no significant differences in heart rate, CO, MAP, CVP, and PAP for horses ventilated with FLEX or VCV (**Table 1**). Dobutamine and fluid requirements as well as isoflurane concentrations were not different between groups.

Horses ventilated using FLEX showed significantly higher Pao₂ and C_{dyn} values compared to horses ventilated with VCV (**Figures 1 and 2**). When switching from FLEX to VCV, the Pao₂ as well as C_{dyn} decreased significantly. In contrast, changing from VCV to FLEX resulted in an increase in both Pao₂ and C_{dyn} values over time.

Horses ventilated by use of FLEX had lower PIP and plateau airway pressure values (**Figures 3 and 4**) and significantly higher P_{mean} (**Figure 5**) when compared to VCV.

Table 1—Mean and SD (SD) of mean arterial blood pressure (MAP), pulmonary arterial pressure (PAP), central venous pressure (CVP), heart rate (HR), and cardiac output (CO) of 8 horses ventilated either for 90 minutes using FLEX and then switched to conventional volume-controlled ventilation (VCV) for 90 minutes (FLEX to VCV) or the same horses ventilated for 90 minutes using VCV and then switched to FLEX for 90 minutes (VCV to FLEX).

Time	MAP (mm Hg)				PAP (mm Hg)				CVP (mm Hg)				HR (beats/min)				Time	CO (L/min)			
	FLEX to VCV		VCV to FLEX		FLEX to VCV		VCV to FLEX		FLEX to VCV		VCV to FLEX		FLEX to VCV		VCV to FLEX			FLEX to VCV		VCV to FLEX	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD		Mean	SD	Mean	SD
10	83	11	80	10	22	5	20	4	12	4	10	5	29	5	31	4	15	34	3	32	4
20	85	11	79	9	21	6	22	5	8	5	9	6	29	4	30	4					
30	82	11	79	8	22	6	22	3	8	5	9	5	29	3	30	3	30	33	4	35	6
40	82	10	79	9	22	3	22	4	8	4	9	4	29	3	30	2	45	33	3	30	5
50	83	11	79	9	22	3	21	3	8	5	8	5	29	2	30	3					
60	79	10	80	10	22	4	21	5	8	3	9	5	29	2	30	2	60	33	4	32	4
70	75	9	81	9	22	4	21	5	8	4	10	3	29	2	30	2	75	34	5	33	4
80	76	9	80	9	22	5	22	4	8	5	9	6	29	1	30	2					
90	75	8	81	10	20	6	20	3	8	3	9	4	30	2	30	2	90	33	3	34	3
100	77	9	80	10	21	4	20	3	8	3	9	5	31	3	30	2	105	34	3	32	2
110	77	9	81	11	21	3	22	5	9	4	9	4	31	3	30	2					
120	77	11	79	10	23	4	23	7	8	5	9	5	31	3	31	3	120	34	3	35	4
130	77	11	77	9	22	5	22	3	8	4	9	3	31	4	30	1	135	34	3	34	5
140	80	12	75	9	22	6	22	2	9	3	9	2	32	5	30	1					
150	79	10	77	9	20	3	21	5	9	3	9	5	31	4	31	3	150	34	4	32	3
160	81	10	77	9	21	4	20	2	9	5	9	4	32	4	31	2	165	34	3	33	4
170	80	11	77	10	20	5	22	3	9	5	9	3	31	4	30	3					
180	79	11	76	10	22	3	22	5	8	6	9	5	31	4	30	2	180	33	4	33	4

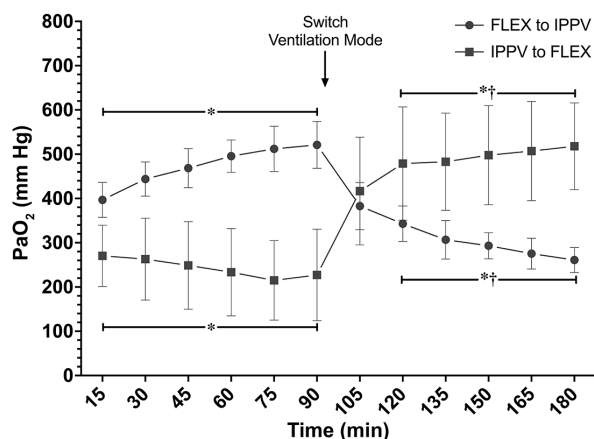


Figure 1—Mean and SD of the P_{aO_2} in 8 horses ventilated either for 90 minutes by use of flow-controlled expiration (FLEX) and then switched to conventional volume-controlled ventilation (VCV) for 90 minutes (FLEX to VCV; circles) or the same horses ventilated for 90 minutes by use of VCV and then switched to FLEX for 90 minutes (VCV to FLEX; squares). *Significant difference between groups. †Significant difference to time point 90 minutes within the same group. IPPV = Intermittent positive-pressure ventilation.

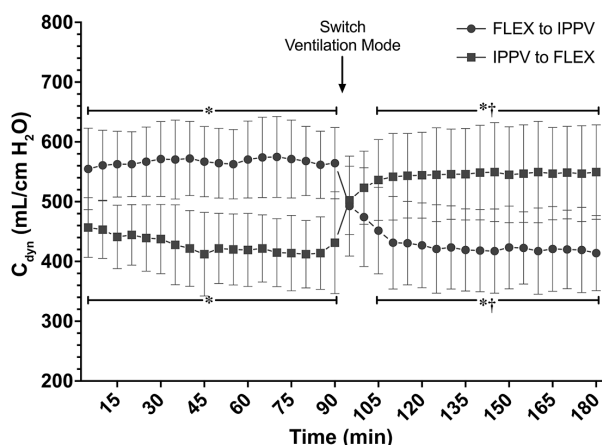


Figure 2—Mean and SD of the dynamic lung compliance (C_{dyn}) in 8 horses ventilated either for 90 minutes by use of FLEX and then switched to conventional VCV for 90 minutes or the same horses ventilated for 90 minutes by use of VCV and then switched to FLEX for 90 minutes. **See** Figure 1 for remainder of key.

Discussion

Our study was designed to evaluate the effects of a FLOW-controlled expiration mode with short FLEX on respiratory mechanics and gas exchange as well as on cardiovascular parameters in healthy, anesthetized horses.

To the authors knowledge, this is the first study describing the use of a piston-driven ventilator to implement FLEX ventilation and the first report about FLEX ventilation in horses. In human medicine and for experimental animal models, pneumatic ventilators are used and the FLEX-ventilation mode is implemented by use of a computer-controlled linear motor adjusting the resistance during expiration. In these studies,^{20,21} the

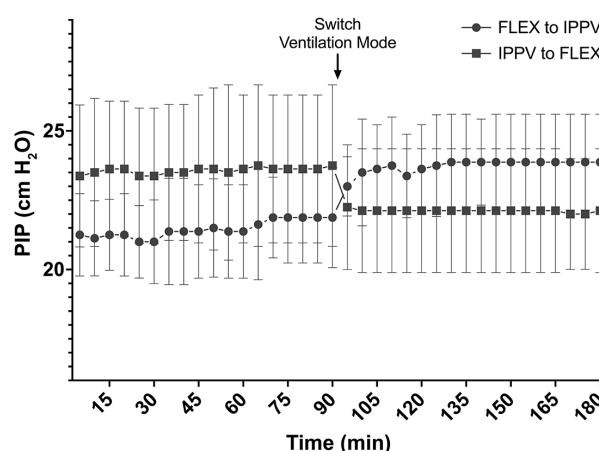


Figure 3—Mean and SD of the peak inspiratory pressure (PIP) in 8 horses ventilated either for 90 minutes by use of FLEX and then switched to conventional VCV for 90 minutes or the same horses ventilated for 90 minutes by use of VCV and then switched to FLEX for minutes). **See** Figure 1 for remainder of key.

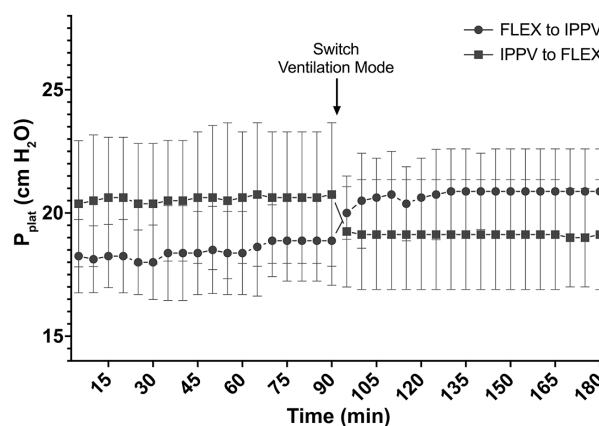


Figure 4—Mean and SD of the plateau airway pressure (P_{plat}) in 8 horses ventilated either for 90 minutes by use of FLEX and then switched to conventional VCV for 90 minutes or the same horses ventilated for 90 minutes by use of VCV and then switched to FLEX for 90 minutes. **See** Figure 1 for remainder of key.

motor modified the cross section of an air duct via partial occlusion with a movable cone, and the position of the cone determined additional expiratory resistance generated by the FLEX device. For our study, we reprogrammed a piston-driven ventilator to release the pressure in a linear way during expiration by moving the piston linearly back to its starting point. In doing so, we had to consider the following: 1) volume losses during the inspiration phase resulting from possible leaks and 2) possible generation of auto PEEP due to high fresh gas flows. To account for volume losses during inspiration, the expiration cycle was immediately interrupted when zero pressure was sensed by the ventilator during the expiration phase and the piston was stopped moving. The machine would drop back to the servo mode for 500 ms. In that time, the machine would change servo to the reference pressure, which in this instance was atmospheric at the end of every cycle

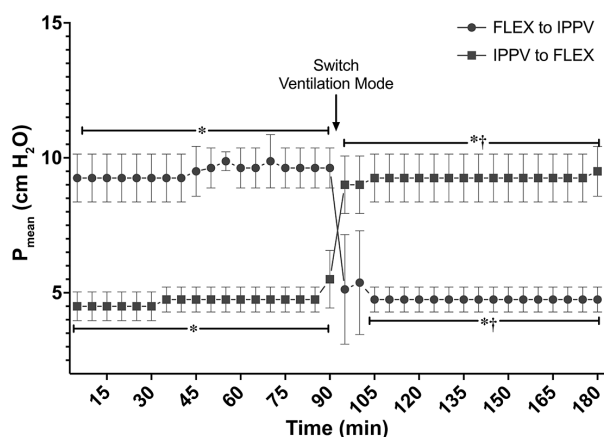


Figure 5—Mean and SD of the mean airway pressure (P_{mean}) in 8 horses ventilated either for 90 minutes by use of FLEX and then switched to conventional VCV for 90 minutes or the same horses ventilated for 90 minutes by use of VCV and then switched to FLEX for 90 minutes. **See** Figure 1 for remainder of key.

to prevent auto-PEEP generation and ensure an end-expiratory pressure of 0 cm H₂O.

The main finding of this study was that horses ventilated with FLEX had significantly higher P_{aO_2} values. This indicates that less atelectasis formation occurred in these horses and therefore more lung areas contributed to ventilation and gas exchange.²² Although the mechanism for this effect is not fully understood, 1 possibility is that FLEX stabilized dependent lung areas and prevented these lung areas from collapse during (late) expiration.²³ A study¹⁹ of anesthetized human patients for neurosurgery indicated that FLEX can cause significant shifts of ventilation from nondependent to dependent lung regions. These authors described increases in dependent lung ventilation and decreased ventilation of nondependent lung areas when FLEX was used.¹⁹ In anesthetized horses, this shift from nondependent to dependent lung areas was seen during alveolar recruitment and is also associated with improvements in ventilation-perfusion matching and oxygenation.²⁴

Another explanation for the occurrence of lesser atelectasis is the specific pressure profile of FLEX ventilation producing a linear, slower decrease of the pressure during expiration. There is a time effect of alveolar collapse, as proposed by a mathematical alveolar model, which postulates that a population of alveoli that close “in a matter of seconds or less” after alveolar pressure is below closing pressure.²⁵ The FLEX-induced slow pressure decrease resulted in longer maintenance of alveolar pressure above closing pressure during expiration. Consequently, the percentage of expiration time at which the alveolar pressure is below closing pressure is significantly lower compared to results at conventional passive expiration; thus, there is less time for the alveoli to collapse. Therefore, FLEX changed the dynamics of expiration fundamentally compared to passive expiration; the lungs stayed in tidal motion for a longer period of time, which can be considered being more

physiological because it is closer to the spontaneous breathing pattern.

Horses ventilated with FLEX had significantly higher C_{dyn} values compared to control horses. Lung compliance is defined as the change in lung volume for 1-U change in transalveolar pressure, with the C_{dyn} of this change measured in the presence of gas flow.²⁶ Certain pulmonary impairments can influence changes in lung compliance such as the formation of atelectasis.²⁷ In the case of atelectasis, pulmonary compliance decreases due to a decrease in lung volume and higher pressures are necessary to inflate the alveoli.²⁷ Therefore, we conclude that the improvement in C_{dyn} further indicates a reduction of atelectasis and more complete lung ventilation.

These results (both improvement of P_{aO_2} and C_{dyn}) show that FLEX ventilation improves the distribution of inspired ventilation as a consequence of more uniform homogeneous lung emptying during expiration and can be used in adult horses under controlled mechanical ventilation during general anesthesia to improve respiratory mechanics, ventilation, and oxygenation.

During conventional expiration, lung emptying is rapid with a sudden pressure drop. In contrast, FLEX decreased early expiratory peak flow and increased late expiratory flow. Consequently, FLEX increased P_{mean} by almost 5 cm H₂O in our horses.

Studies in anesthetized horses have shown that increasing the airway pressures can result in a decrease of cardiac index and arterial blood pressure.¹⁰ The physiologic mechanism involved in the reduction of CO has been ascribed to a decrease in the filling pressure of the right heart.^{28,29} Early studies of humans showed a negative correlation between increased airway pressures and circulation parameters,²⁸ and in horses, high end-expiratory pressures can produce pronounced cardiovascular depression.^{10,30} In our study, we found no FLEX-dependent effects on hemodynamics compared to conventional ventilation despite increasing the P_{mean} . This is in concordance with studies in pigs²⁰ and human patients¹⁹ that showed no effects of FLEX on blood pressure, central venous pressure, CO, or catecholamine demand. In alignment with these studies our results support our hypothesis that FLEX is hemodynamically neutral compared to conventional ventilation modes in anesthetized horses.

One limitation of our study was the lack of a group of horses ventilated by use of PEEP with alveolar recruitment maneuver (ARM). Alveolar recruitment was not applied during the experiment because this might have masked the effects of FLEX ventilation. Recruiting nonventilated lung areas with an ARM and subsequent application of sufficient PEEP to preserve ventilation of reopened alveoli is an established ventilation strategy for horses and is employed to minimize pulmonary complications while improving pulmonary gas exchange and thus arterial oxygenation.^{9,11,12,24,30} In further studies, it will be interesting to compare the efficacy of FLEX ventilation to PEEP ventilation with ARM and to evaluate whether lesser PEEP can be used in FLEX-ventilated horses. Some studies performed in pigs already indicate that lower PEEP levels can be applied when FLEX ventilation is used.¹⁹ In anesthetized

horses, there is a linear correlation between airway pressures and CO₁₀. Therefore, a possible reduction in PIP and PEEP might lead to more cardiovascular stability and less cardiovascular compromise.¹⁰

Another limitation was that our study was conducted with healthy, normovolemic horses. It will be necessary to assess whether FLEX ventilation can safely be performed in cardiovascularly compromised patients and if it will be as effective in patients with ventilatory impairments.

In conclusion, our results show that FLEX ventilation can be performed in horses after modification of a piston-driven ventilator and that it results in significant improvements of the Pao₂ and C_{dyn} without compromising the cardiovascular system when compared to conventional ventilation in horses. Further studies shall elucidate whether FLEX results in better oxygenation compared to PEEP ventilation with alveolar recruitment, particularly in clinical settings.

Acknowledgments

This study was supported by the USDA Formula Fund (No. 1027655) of the National Institute of Food and Agriculture.

The authors declare that there were no conflicts of interest.

References

- Dugdale AH, Taylor PM. Equine anaesthesia-associated mortality: where are we now? *Vet Anaesth Analg*. 2016;43(3):242–255.
- Costa-Farré C, Prades M, Ribera T, Valero O, Taurà P. Does intraoperative low arterial partial pressure of oxygen increase the risk of surgical site infection following emergency exploratory laparotomy in horses? *Vet J*. 2014;200(1):175–180.
- Johnston GM, Eastment JK, Wood JLN, Taylor PM. The confidential enquiry into perioperative equine fatalities (CEPEF): mortality results of phases 1 and 2. *Vet Anaesth Analg*. 2002;29(4):159–170.
- Nyman G, Funkquist B, Kvart C, et al. Atelectasis causes gas exchange impairment in the anaesthetised horse. *Equine Vet J*. 1990;22(5):317–324.
- Sorenson PR, Robinson NE. Postural effects of lung volumes and asynchronous ventilation in anaesthetized horses. *J Appl Physiol Respir Environ Exerc Physiol*. 1980;48(1):97–103.
- Hedenstierna G, Nyman G, Frostell C. Animal models of lung physiology during anaesthesia. In: Hau J, Van Hooser GL, eds. *Handbook of Laboratory Animal Science*. 2nd ed. CRC Press; 2005:263–288.
- Stack A, Derksen FJ, Williams KJ, Robinson NE, Jackson WF. Lung region and racing affect mechanical properties of equine pulmonary microvasculature. *J Appl Physiol*. 2014;117(4):370–376.
- Nyman G, Hedenstierna G. Ventilation-perfusion relationships in the anaesthetised horse. *Equine Vet J*. 1989;21(4):274–281.
- Hopster K, Käestner SBR, Rohn K, Ohnesorge B. Intermittent positive pressure ventilation with constant positive end-expiratory pressure and alveolar recruitment manoeuvre during inhalation anaesthesia in colic horses and the influence on the early recovery period. *Vet Anaesth Analg*. 2011;38(3):169–177.
- Hopster K, Wogatzki A, Geburek F, Conze P, Käestner SBR. Effects of positive end-expiratory pressure titration on intestinal oxygenation and perfusion in isoflurane anaesthetized horses. *Equine Vet J*. 2017;49(2):250–256.
- Hopster K, Rohn K, Ohnesorge B, Käestner SBR. Controlled mechanical ventilation with constant positive end-expiratory pressure and alveolar recruitment manoeuvres during anaesthesia in laterally or dorsally recumbent horses. *Vet Anaesth Analg*. 2017;44(1):121–126.
- Wettstein D, Moens Y, Jaegglin-Schmucker N, et al. Effects of an alveolar recruitment maneuver on cardiovascular and respiratory parameters during total intravenous anesthesia in ponies. *Am J Vet Res*. 2006;67(1):152–159.
- Lessard MR, Guérot E, Lorino H, Lemaire F, Brochard L. Effects of pressure-controlled with different I:E ratios versus volume-controlled ventilation on respiratory mechanics, gas exchange, and hemodynamics in patients with adult respiratory distress syndrome. *Anesthesiology*. 1994;80(5):983–991.
- Campbell RS, Davis BR. Pressure-controlled versus volume-controlled ventilation: does it matter? *Respir Care*. 2002;47(4):416–424.
- Maeda Y, Fujino Y, Uchiyama A, Matsuura N, Mashimo T, Nishimura M. Effects of peak inspiratory flow on development of ventilator-induced lung injury in rabbits. *Anesthesiology*. 2004;101(3):722–728.
- Grasso S, Fanelli V, Cafarelli A, et al. Effects of high versus low positive end-expiratory pressures in acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2005;171(9):1002–1008.
- Tremblay LN, Slutsky AS. Ventilator-induced lung injury: from the bench to the bedside. *Intensive Care Med*. 2006;32(1):24–33.
- Pinhu L, Whitehead T, Evans T, Griffiths M. Ventilator-associated lung injury. *Lancet*. 2003;361(9354):332–340.
- Wirth S, Springer S, Spaeth J, Borgmann S, Goebel U, Schumann S. Application of the novel ventilation mode FLOW-controlled EXpiration (FLEX): a crossover proof-of-principle study in lung-healthy patients. *Anesth Analg*. 2017;125(4):1246–1252.
- Goebel U, Haberstroh J, Foerster K, et al. Flow-controlled expiration: a novel ventilation mode to attenuate experimental porcine lung injury. *Br J Anaesth*. 2014;113(3):474–483.
- Schumann S, Goebel U, Haberstroh J, et al. Determination of respiratory system mechanics during inspiration and expiration by FLOW-controlled EXpiration (FLEX): a pilot study in anesthetized pigs. *Minerva Anesthesiol*. 2014;80(1):19–28.
- Lachmann B. Open the lung and keep the lung open. *Intensive Care Med*. 1992;18(6):319–321.
- Schmidt J, Wenzel C, Mahn M, et al. Improved lung recruitment and oxygenation during mandatory ventilation with a new expiratory ventilation assistance device. *Eur J Anaesthesiol*. 2018;35(10):736–744.
- Ambrisko TD, Schramel J, Hopster K, Kaestner S, Moens Y. Assessment of distribution of ventilation and regional lung compliance by electrical impedance tomography in anaesthetized horses undergoing alveolar recruitment manoeuvres. *Vet Anaesth Analg*. 2017;44(2):264–272.
- Smith BJ, Grant KA, Bates JH. Linking the development of ventilator-induced injury to mechanical function in the lung. *Ann Biomed Eng*. 2013;41(3):527–536.
- Marshall R. The physical properties of the lungs in relation to the subdivisions of lung volume. *Clin Sci*. 1957;16(3):507–515.
- Duggan M, Kavanagh BP. Pulmonary atelectasis: a pathogenic perioperative entity. *Anesthesiology*. 2005;102(4):838–854.
- Cournand A, Motley HL. Physiological studies of the effects of intermittent positive pressure breathing on cardiac output in man. *Am J Physiol*. 1948;152(1):162–174.
- Lenfant C, Howell BJ. Cardiovascular adjustments in dogs during continuous pressure breathing. *J Appl Physiol*. 1960;15:425–428.
- Wilson DV, Soma LR. Cardiopulmonary effects of positive end-expiratory pressure in anesthetized, mechanically ventilated ponies. *Am J Vet Res*. 1990;51(5):734–739.

Supplementary Materials

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