--- Today's Date ---

06/28/2023

--- Name of 501(c)(3) Organization ---

University of Pennsylvania School of Veterinary Medicine

--- Federal Tax-Exempt ID# ---

23-1352685

--- Year Established ---

1740

--- Amount Requested ---

15,348.00

--- Name of Executive Director ---

Elizabeth Peloso

--- Mailing Address ---

3541 Walnut St Franklin Bldg. 5th Floor
Philadelphia, PA
19141

--- Email address ---

pennaors@lists.upenn.edu

--- Work Phone # ---

+12158987293

--- Organization's website ---

https://researchservices.upenn.edu

--- Link to Organization's most recent filed IRS Financial Statements (#990): ---

https://apps.irs.gov/pub/epostcard/cor/231352685_202106_990_2022071120200882.pdf

--- Upload Organization's most recent filed IRS Financial Statements (#990) ---

https://www.terfusa.org/wp-content/uploads/wpforms/809-8fba8c278fa5e5fb5fb2cbe55842a214/Trustees-2020-Form-990-FY21-PD-5fefa85eae35380379005f1c746e5638.pdf

--- Farm/Facility Name ---

New Bolton Center

--- Farm/Facility Physical Location (City, State, Zip) ---

Kennett Square

--- Farm/Facility Mailing Address ---

382 West Street Road
Kennett Square, PA
19348

--- Contact Name and Title ---

Dr. Klaus Hopster, PhD, Associate Professor of Large Animal Anesthesia

--- Contact Work Phone ---

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--- Contact Email ---

khopster@upenn.edu

--- 1. Brief mission statement and describe the distinguishing features of your organization that supports the mission of TERF and the relevance to this proposal. ---

Safe performance of surgical procedures on horses often requires general anesthesia, a procedure unfortunately associated with a high mortality rate. Peri-anesthetic mortality is due, in part, to pulmonary pathophysiologic features arising from hypoxemia that can occur during prolonged periods of anesthesia and recumbency. While controlled ventilation techniques to keep the lungs ventilated have been developed to reduce such complications, the large weight of the abdominal viscera of the horse that lies directly on the diaphragm during recumbency increases the risk of hypoxemia resulting from compression atelectasis in non-aerated lung areas. In addition, the lower lung fields - that are preferentially perfused during recumbency - are also the most affected by the abdominal pressure and therefore have the highest risk for collapse.
As intraoperative hypoxemia and lung-collapse are associated with the high mortality and morbidity, with prolonged intensive care unit and hospital stays as well as with altered performance of these horses after general anesthesia due to increased rates of respiratory failure and pneumonia, strategies that improve oxygenation in horses undergoing general anesthesia are required to reduce intra- and postoperative complications.

Since the beginning of my career, I was most interested in equine pulmonary physiology and pathophysiology. During my inaugural thesis, my PhD, and later my habilitation thesis my research strongly focused on the development of new strategies to prevent pulmonary ventilation mismatching and improving gas exchange during general anesthesia. I was involved in the development of multiple ventilation approaches and concepts to improve ventilation and pulmonary mechanics in compromised patients as well as in the development of new technologies and monitor devices, including a thermal-mass flowmeter, to establish and improve non-invasive, real time pulmonary diagnostics.

New Bolton Center`s anesthesia team has the knowledge and equipment (including a unique large animal piston-driven ventilator) to contribute to a solution and to initiate the next steps of anesthesia ventilation advancements to reduce the number of horses lost every year due to anesthesia related respiratory complications.

--- 2. Briefly outline 3-5 goals for the requested funds and how these goals support your mission. ---

- Software development and modification of the existing large animal piston-driven ventilator
- Better understanding of the changes of respiratory mechanics of the equine lung during general anesthesia and controlled ventilation
- Improvement of the gas exchange and oxygenation of horses during general anesthesia
- Reduction of general anesthesia related risks in horses

--- 3. Provide a detailed description of the proposed project, how it is related to the mission of TERF and how it will impact the health and welfare of the horse. (Note: research applications should be understandable to a non-scientific audience and include sufficient detail and rigor for the scientific reviewers.) ---

Traditionally, mechanical ventilation is achieved via active lung inflation during inspiration and passive lung emptying during expiration. Multiple studies, including our own, have shown that high inspiratory pressures followed by sustained positive end-expiratory pressures (PEEP) can improve gas exchange in anesthetized patients (Hopster et al. 2011; Hopster et al. 2016; Hopster et al. 2017; Wettstein et al. 2006). However, positive pressure provided during mechanical ventilation can cause ventilator-induced lung injury even in healthy subjects as a consequence of an imbalance between lung stress and strain (Kuchnicka et al. 2013). In addition, excessive PEEP can impair cardiovascular function by compressing the vena cava and reducing venous return to the heart, leading to reduced stroke volume and cardiac output (Hopster et al. 2017), clearly undesirable outcomes.
Currently, the expiration phase in nearly all mechanical ventilation modes is passive and therefore governed by the mechanical characteristics of the respiratory system. However, prolonging the expiration phase represents a potentially powerful and innovative way to improve oxygenation. Indeed, the FLow-controlled EXpiration (FLEX) mode was recently introduced as an approach to lung-protective ventilation (Schumann et al. 2014; Goebel et al. 2014; Hopster et al. 2022). FLEX modulates the otherwise passive expiration phase: reducing the initial high-expiratory peak flow and causing expiratory gas flow to persist throughout the expiratory phase. In studies of human patients, FLEX increased ventilation in the dorsal-dependent lung regions, thereby homogenizing the ventilation distribution (Wirth et al. 2017) and improving the distribution of gas flow and ventilation at the consecutive breath. Moreover, in an animal model of acute respiratory distress syndrome, FLEX reduced ventilation-induced lung damage, decreased severity of pulmonary edema and focal inflammation, increased dynamic compliance, and improved ventilation. (Goebel et al. 2014). Notably, FLEX ventilation is predicted to be

even more beneficial for patients with large body mass, as their expiration is relatively rapid compared with that in patients with high compliance or lower body mass (Tremblay and Slutsky 2006).

Purpose: We will test the hypothesis that FLEX will be particularly advantageous in horses undergoing surgery, decreasing the occurrence of intraoperative hypoxemia and lung-collapse and reducing impairments of cardiovascular function that can occur following excessive ventilation pressure.
Our group has done extensive work in the modification of lung-protective ventilation modes. As part of these studies we developed strategies to evaluate lung aeration and ventilation as well as ventilation-perfusion ratios (Hopster et al. 2011; Hopster et al. 2016; Hopster et al. 2017; Hopster et al. 2022). During these studies we developed a close relationship with the manufacturing engineers and IT specialists of the piston-driven ventilator Tafonius. Notably, my group recently developed a computer program to control the piston movement and positioning of this piston-driven ventilator, thus allowing us to program individual and adapted ventilation modes. These are exciting findings and our group is the first to evaluate the modification of the expiratory phase of a ventilatory cycle using the piston-driven ventilator model. As multiple studies have shown the importance of the expiratory phase for the development/prevention of hypoxemia (Hopster et al. 2011; Goebel et al. 2014; Hopster et al. 2016) the logical next step to improve ventilation-perfusion-matching is the application of FLEX ventilation.

Methods to be used and work to be undertaken:
A conventional ventilator releases the gas flow during expiration very rapidly, which results in a fast drop in pressure (Figure 1) during expiration (green). In preliminary studies, we have modified the software of the large animal piston-driven ventilator Tafonius using “Phase Editor” software. Specifically, the ventilator was programmed to release the pressure in a more linear pattern (Figure 2) during expiration (green). After successful modification of the mechanics and a configuration and update of the controlling software the FLEX-ventilation mode was applied to an artificial lung consisting of two 55-gallon polyethylene barrels, the compliance of which is comparable to the compliance of a healthy horse with a body weight of approximately 550 kg. Preliminary results showed an improvement of the compliance of the artificial lung when ventilated with FLEX compared to conventional pressure ventilation, resulting in a significantly lower mean ventilation pressure. Together, these results support feasibility for the proposed studies.

Specific objectives/aims
Phase 1: Modification of a piston-driven ventilator and establishment of configurations and settings to apply flow-controlled expiration (FLEX) in large animals.
Phase 2: Evaluate the effects of the new FLEX-ventilation mode on pulmonary mechanics and arterial oxygenation in anesthetized, healthy horses.

Aim 1 We developed a software prototype able to modify the moving pattern of a piston driven large animal ventilator to allow for linear release of the delivered tidal volume. In summary, the ventilator was programmed to release the delivered tidal volume in a linear fashion instead of servoing to zero pressure during exhalation by measuring the inspired volume and calculating the time it takes to exhale it at a constant rate. While our preliminary data support feasibility, further evaluation and testing are necessary to optimize the FLEX-ventilation mode. Using an artificial lung model, we will utilize the FLEX mode with different volumes, pressures, cycle times and percentage of FLEX and evaluate its effects on static and dynamic compliance of the artificial lung. We will specifically identify the shortest cycle time and lowest pressure that provide suitable improvements in compliance of the artificial lung, with the ultimate goal of identifying the safest settings with regards to inspiration and expiration time and tidal volume for an equine lung.

Aim 2 Using the optimized settings identified above, the FLEX mode will be tested in healthy, experimental horses in a prospective randomized crossover setting. A statistical a priori power analysis (Type II error = 0.2; Type I error = 0.05) showed that 8 animals will be necessary to detect clinically significant changes in arterial oxygenation and lung compliance, assuming a standard deviation of 15%. In this phase of the study, we expect to observe obvious advantages of FLEX ventilation on pulmonary mechanics and will further determine effects of the ventilation mode on the cardiovascular system.

All animals will be anesthetized using a standard protocol similar to what is used in clinical patients. All horses will be ventilated in dorsal recumbency using conventional volume-controlled ventilation (VCV) as well as two different modes of FLEX ventilation (FLEX50 = linear emptying of the lung over 50% of the expiratory time; FLEX100 = linear emptying of the lung over 100% of the expiratory time) for 60 minutes each in randomized order. Respiratory mechanics and arterial oxygenation as well as cardiovascular status will be compared between these three groups. In particular the peak, plateau and mean airway pressures, dynamic lung compliance, pulmonary hysteresis/hysteresis ratio as well as the normalized maximal distance ratio will be measured, and arterial blood pressure, cardiac output and blood gases analyzed.

To evaluate to effects of each ventilation mode on the cardiovascular system the mean arterial blood pressure, the central venous blood pressure and the cardiac output will be measured and compared.

Data analysis will be performed in consultation with Dr. Darko Stefanovski who is a statistician at the University of Pennsylvania. Data will be analyzed using the statistical software SAS 9.3 (SAS Institute Inc., NC, USA) and GraphPad Prism Version 7 (GraphPad Software, Inc. USA). Visual assessment of qq-plots and the Shapiro-Wilk test will be used to confirm normal distribution of model residuals of dependent variables. Variables will be compared to baseline and between groups. Statistical analysis will be undertaken in terms of a two-factorial variance analysis for repeated measurements, Bonferroni correction for multiple comparisons and mixed-effects linear regressions. The level of significance will be set to 5 % ($p < 0.05$).

Expected Results: Our preliminary results are very promising and showed that the software developed is capable of programming the Tafonius to implement the FLEX mode. We are confident that we will now be able to optimize these settings with regards to applied volumes, expiration times and flow rates in our artificial lung model. We expect to show that application of FLEX improves the pulmonary mechanics and arterial oxygenation in anesthetized horses. However, cardiovascular effects in anesthetized horses remain the biggest challenge and if the FLEX mode causes significant alterations in blood pressure or cardiac output, further alterations of the controlled expiration (exponentially declining, longer expiratory pause) will need to be considered to achieve cardiovascular stability. A successful modification of the expiratory phase would be a groundbreaking advancement in establishing and maintaining ventilation-perfusion-matching under general anesthesia.

The FLEX ventilation mode has the potential to change the veterinary (particularly large animals) approach of controlled ventilation; indeed, large animals may be an informative model to investigate the effects of FLEX on patients with high body mass. We will use the obtained results and this approach to study the effects of long-term ventilation with and without end-expiratory pressure on pulmonary function and inflammatory responses. Obtained results would enhance our capacity to attract further funding.

--- 4. Provide a timeline detailing the expected progress of the project and specific milestones. ---

• Month 1 and 2: Preparation, purchase of equipment, recruitment of horses from the research and teaching herd at New Bolton Center • Month 3 to 8: Performing experiments and data acquisition • Month 9 to 10: Data analysis • Month 11 to 12: Summary of results and main findings; creating a report

--- 5. Provide a detailed budget for the projected use of the funds. (Note: no funds will be provided for administrative overhead or capital spending; TERF reserves the right to modify funding based on Foundation requirements). Attach budget to submitted proposal as needed. ---

ANIMALS (Use & Care) Cost
Animal purchase $0.00
Animal per diem ($49 per day, 8 horses 15 days each, 120 days total) $5,880.00

SUPPLIES
Anesthetic drugs ($465 per anesthetic event) $3,720.00 Catheters for cardiac output measurements ($75 per horse) $600.00
Miscellaneous $1,000.00

OTHER EXPENSES
Software update/ modifications $2,900.00 Blood gas analysis ($26 per sample, 6 samples per anesthetic event) $1,248.00

TOTAL COSTS $15,348.00

--- 6. Provide a list of all other sources of funding and the amount(s) received. ---

Comprehensive understanding of the effects of the TCAV method in horses.
Harr M. Zweig Memorial Fund for Equine Research Cornell University
02/2023 – 12/2024 Co-investigator 5 %, $ 163,196

Influence of General Anesthesia on the Equine Lung Microbiome Raymond Firestone Trust Research Grant, Department of Clinical Studies – UPenn
02/2023 – 01/2024 Principal-investigator 5 %, $ 6,545

Effects of volatile anesthetic drugs on the lung airway immune cell functions in horses Raymond Firestone Trust Research Grant, Department of Clinical Studies – UPenn
02/2023 – 02/2024 PG Co-investigator 5 %, $ 11,350

Effects of FLEX time on pulmonary mechanics in horses undergoing general anesthesia.
USDA formula Funding, U.S. Department of Agriculture
06/2023 – 9/2024 Principal-investigator 5 %, $ 17,200

--- 7. Briefly summarize your charity's past public education and research efforts. ---

not applicable

--- 8. If you received funding from TERF previously, describe how these funds were used and outcomes achieved. Include any relevant publicity your charity received relating to the funding. (i.e.: media coverage, such as news articles, scientific publications, provide links to copies, as appropriate). ---

not applicable

--- 9. List other organizations or major contributors that have provided funding to your organization in the last calendar/fiscal year. For research grant applications, provide a list of all current funding relating to your current proposal. ---

Harr M. Zweig Memorial Fund for Equine Research Cornell University

Raymond Firestone Trust Research Grant, Department of Clinical Studies – University of Pennsylvania

USDA formula Funding, U.S. Department of Agriculture

--- 10. Name a responsible person with whom TERF may communicate regarding specific questions and who will be responsible for follow-up information regarding the project. ---

Klaus Hopster

--- 11. Provide appropriate references to support the proposed research. ---

Goebel U, Haberstroh J, Foerster K, Dassow C, Priebe H, Guttmann J, et al. Flow-controlled expiration: a novel ventilation mode to attenuate experimental porcine lung injury. Br J Anaesth 2014;113(3):474.

Hopster K, Hurcombe SD, Simpson K, VanderBroek AR, Driessen B. Flow-controlled expiration improves respiratory mechanics, ventilation, and gas exchange in anesthetized horses. Am J Vet Res 2022;83(5):393-398.

Hopster K, Kästner SB, Rohn K, Ohnesorge B. Intermittent positive pressure ventilation with constant positive end-expiratory pressure and alveolar recruitment manoeuvre during inhalation anaesthesia in horses undergoing surgery for colic, and its influence on the early recovery period. Vet Anaesth and Analg 2011;38(3):169-177.

Hopster K, Rohn K, Ohnesorge B, Kästner SBR. Controlled mechanical ventilation with constant positive end-expiratory pressure and alveolar recruitment manoeuvres during anaesthesia in laterally or dorsally recumbent horses. Vet Anaesth and Analg 2017;44(1):121-126.

Hopster K, Wogatzki A, Geburek F, Conze P, Kästner SBR. Effects of positive end-expiratory pressure titration on intestinal oxygenation and perfusion in isoflurane anaesthetised horses. Equine Vet J 2016;49(2):250.

Kuchnicka K, Maciejewski D. Ventilator-associated lung injury. Anaesthesiol Intensive Ther. 2013;45(3):164-70.

Schumann S, Goebel U, Haberstroh J, Vimlati L, Schneider M, Lichtwarck-Aschoff M, 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.

Tremblay LN, Slutsky AS. Ventilator-induced lung injury: from the bench to the bedside. Intensive Care Med 2006;32(1):24-33.

Wettstein D, Moens Y, Jaeggin-Schmucker N, Bohn SH, Ulrich Rothen H, Mosing M, 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.

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.

--- 12. How many Executive Staff and Board of Directors does your organization have? ---

52

--- Director Name (1) ---

https://secretary.upenn.edu/trustees-governance/trustees

--- Director Address (1) ---

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