

# FLEX Ventilation Improves Pulmonary Function in a Rib-Tethered Mini-Pig Model of Thoracic Insufficiency Syndrome

Carly Ciociola<sup>1</sup>, Jerrienne Brandy<sup>1</sup>, Klaus Hopster<sup>1</sup>, Madeline Boyes<sup>1</sup>, Agathe Guillemet<sup>1</sup>, Oscar H. Mayer<sup>2</sup>, Alexander I. Gipsman<sup>2</sup>, Brian Snyder<sup>3</sup>, Thomas P. Schaefer<sup>1</sup>, Patrick Cahill<sup>2</sup>

<sup>1</sup>Department of Clinical Studies New Bolton Center, University of Pennsylvania School of Veterinary Medicine, Kennett Square PA, <sup>2</sup>Children's Hospital of Philadelphia, Philadelphia PA, <sup>3</sup>Boston Children's Hospital, Boston MA  
[ciociol1@vet.upenn.edu](mailto:ciociol1@vet.upenn.edu)

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**INTRODUCTION:** In children with early onset scoliosis (EOS), the spine and associated rib cage deformities often result in thoracic insufficiency syndrome (TIS), where anatomic constriction of the thorax prevents uniform lung inflation and impedes lung growth, leading to extrinsic restrictive lung disease. A restrictive chest wall results in reduced respiratory system compliance, hypoventilation, hypoxemia, and significant morbidity with respiratory tract infections [2]. Untreated, children with TIS develop progressive respiratory and cardiovascular functional impairments, culminating in pulmonary hypertension and increased mortality [1]. Experimental models to study the pathophysiology and treatment of TIS remain limited. A rib-tethered large animal model simulating progressive scoliosis and thoracic deformity enables longitudinal evaluation of pulmonary function. We investigated the effects of a novel ventilation strategy, Flow-controlled Expiration (FLEX) [3,4], on lung function in a scoliotic mini-pig with TIS. The aim of this study was to assess long-term changes in pulmonary compliance and gas exchange in a rib-tethered large animal model of TIS, and to evaluate whether FLEX ventilation improves pulmonary mechanics and ventilation-perfusion matching when compared to conventional pressure ventilation (CPV).

**METHODS:** Under IACUC approval, rib tethering of the right hemithorax was performed in four female and castrated male Yucatan mini-pigs at 8 weeks of age to induce progressive thoracic deformity (Figure 1). Two age- and weight-matched sham-operated animals served as controls. Longitudinal imaging and pulmonary function assessment were conducted over 9 months (cohort 1) and 3 months (cohort 2). CT imaging was used to measure Cobb angle and mean lung volume (MLV). Under general inhalant anesthesia, digital radiographs (DV, Right Lateral and Left Lateral) of the thorax and thoracic Computed Tomography (OmniTom® 8-slice small-bore mobile CT) were obtained. The inspiratory tidal volume (TV) was measured while animals were breathing spontaneously. Dynamic lung compliance (C<sub>dyn</sub>), PaO<sub>2</sub>/FiO<sub>2</sub> ratio, and lung dead space (P<sub>ET</sub>CO<sub>2</sub>/PaCO<sub>2</sub> ratio) were analyzed during CPV and FLEX ventilation. The mean lung volume (MLV) was measured using Sectra PACS software program from CT reconstruction. At study end, animals were anesthetized for pulmonary testing under spontaneous ventilation, CPV, and FLEX. Key endpoints included dynamic lung compliance (C<sub>dyn</sub>), tidal volume (TV), PaO<sub>2</sub>/FiO<sub>2</sub> ratio, and dead space (P<sub>ET</sub>CO<sub>2</sub>/PaCO<sub>2</sub>).

**RESULTS:** The tethered animal in cohort 1 developed a sustained spinal curvature of 25° and marked asymmetry in thoracic growth. Mean MLV and TV in the tethered animals (1586 cm<sup>3</sup> and 290 mL) were markedly lower than in the control (1912 cm<sup>3</sup> and 485 mL) (Figure 2). During CPV, C<sub>dyn</sub> was reduced in the tethered animals (32 mL/cmH<sub>2</sub>O vs 55 mL/cmH<sub>2</sub>O in control animals) and improved by 68% with FLEX. FLEX increased PaO<sub>2</sub>/FiO<sub>2</sub> from 390 mmHg to 468 mmHg and reduced dead space from 18% to 3%, indicating more uniform ventilation and improved gas exchange. In the second cohort, the tethered animals failed to develop sustained spinal curvature and asymmetry in thoracic growth. Despite a lack of scoliosis, MLV and TV in the tethered animals (1,051 cm<sup>3</sup> and 158 mL) were significantly different from those of the control (MLV 1,420 cm<sup>3</sup> and TV 223 mL). During CPV, C<sub>dyn</sub> was reduced in tethered animals (35 mL/cmH<sub>2</sub>O) compared to the control (47 mL/cmH<sub>2</sub>O). C<sub>dyn</sub> improved during FLEX in the tethered (45 mL/cmH<sub>2</sub>O) but not in the control animal. Further, during FLEX, the dead space was markedly reduced (4% during FLEX vs 12% during CPV).

**DISCUSSION:** It is well known that hypoxemia and impaired pulmonary perfusion are common complications in EOS patients with TIS [5]. Longitudinal studies of patients with untreated EOS reveal that 38% of patients die from respiratory failure [6]. Using our large animal untreated scoliosis model, we demonstrate that pulmonary function remains highly affected by chest deformity, likely due to decreased lung volumes and reduced chest compliance. As to why the tethered animals in the cohort without scoliosis still showed lower lung volumes compared to controls, plausible explanations include: Impaired Respiratory Muscle Function, where rib tethering changes the geometry and orientation of the ribs and intercostal muscles, even if a visible spinal curvature never develops. This altered orientation likely compromises the mechanical advantage of the intercostal and accessory respiratory muscles, reducing their efficiency in expanding the thorax during inspiration. As a result, tidal volume and mean lung volume would be reduced, despite preserved overall spinal symmetry. Increased Chest Wall Stiffness, where Rib tethering itself may cause fibrous remodeling, scarring, or altered rib biomechanics that stiffen the thoracic cage. Even in the absence of scoliosis, the rib cage could expand less effectively, producing a restrictive physiology with lower compliance and reduced lung volumes. The fact that dynamic compliance was already reduced during conventional ventilation in the tethered but nonscoliotic pigs suggests that chest wall stiffness is at least part of the explanation. Developmental Effects on Lung Growth - tethering is performed at a young age, when lung growth is tightly coupled to thoracic growth. By physically constraining thoracic expansion—even without scoliosis—the tethering may limit alveolar proliferation and lung parenchymal expansion, resulting in smaller absolute lung volumes later.

**SIGNIFICANCE/CLINICAL RELEVANCE:** Our findings from this and previous studies (Figure 1) confirm that both lung anatomy and function remain altered in the adult Yucatan mini-pig with induced spinal deformity up to two years post-tether. The rib tethering imposes structural restriction (chest wall stiffness and impaired growth) and simultaneously alters muscle mechanics (suboptimal fiber orientation and leverage). Together, these produce a restrictive defect even when overt spinal deformity does not occur. FLEX ventilation improved compliance and reduced dead space in the tethered, scoliotic, and non-scoliotic animals, suggesting that the lungs themselves remain recruitable, but the thoracic cage mechanics are the limiting factor. FLEX ventilation considerably improves lung function and dynamics by homogenizing the distribution of ventilation as well as gas and blood flow during expiration. The modulating and linearization of the expiratory phase further reduce the degree of atelectasis occurring during the second half of the expiratory period. Additionally, this ventilation mode might help optimize lung compliance and gas exchange in children with thoracic deformities undergoing general anesthesia for corrective surgery and be an option in children with TIS requiring long-term non-invasive ventilation.

**REFERENCES:** [1] Butler R, et al, ORS, 2024 [2] Mayer O, et al, CPPAHC, 46(3), 2016. [3] Goebel U, et al. Br J Anaesth, 113:474-483, 2014. [4] Wirth S, et al, Anesth Analg, 125: 1246-1252, 2017. [5] Wang Y, et al, JOSR 18(1), p.246, 2023. [6] Pehrsson K, et al, Spine, 17(9), pp.1091-1096, 1992.

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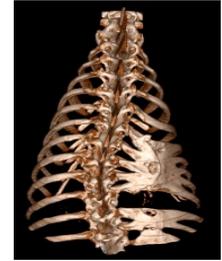


Fig. 1. Dorsoventral 3D CT reconstruction of a tethered animal at 28 months post-op of the right hemithorax showing marked scoliosis.

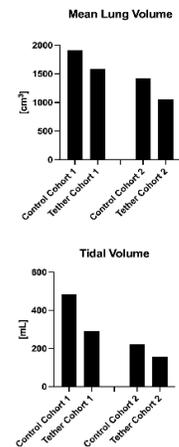


Fig. 2. Mean MLV and TV in the tethered animals (1586 cm<sup>3</sup> and 290 mL) were significantly lower than in the control group (1912 cm<sup>3</sup> and 485 mL).