Dynamic Imaging To Assess Regional Gas Exchange in Pre-clinical Model of Thoracic Insufficiency Syndrome

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INTRODUCTION: Children with early onset scoliosis are often critically ill with failing respiratory function because of associated spine and ribcage deformity. This thoracic dysfunction termed Thoracic Insufficiency Syndrome (TIS) is a manifest by decreased thoracic volume, increased chest wall stiffness, declining vital capacity, and overall failure to thrive. Surgical interventions that allow continued spinal growth while reducing thoracic distortion are promising, however, the respiratory status of these critically ill patients is not consistently improved with simply increasing the space available for the lung to grow. Normal pulmonary growth, defined by gains in lung parenchymal mass and alveolar multiplication occurs until age 8. There is limited clinical data that lung function is favorably impacted if children are treated earlier, predicated on the assumption that treatment delay misses this developmental window of rapid alveolarization. Measurement of pulmonary function in early childhood by spirometry is the gold standard, however, is limited by a patients ability to actively participate with testing. There is an unmet need for new strategies to assess pulmonary function in pediatric patients with TIS to understand the underlying pathophysiology and determine the effectiveness of surgical treatments to preserve and rejuvenate pulmonary function. We set out to evaluate two complementary imaging modalities: 1) hyperpolarized MRI using ^{129}Xe (HXe) gas diffusion to assess lung pathology via regional analysis of gas exchange, and 2) dynamic CT/MRI to quantify dynamic lung volume and shape changes as a function of thoracic and diaphragmatic kinematics during the respiratory cycle under free breathing conditions. Our hypothesis is that non-invasive imaging of respiration and ventilation will reveal specific pathoanatomic changes contributing to respiratory dysfunction.

METHODS: Under IACUC approval, two New Zealand White rabbits were enrolled in the study; one underwent a right sided rib tethering procedure where ribs 3-9 were surgically tethered using #1 FiberWire at 5 weeks of age. The other rabbit was unoperated and used as a litter-mate control. The rabbits were housed in similar conditions and underwent the same imaging timeline with free breathing dynamic CT and HXe MRI at 6, 12, and 30 weeks of age. All images were acquired in sternal recumbency, on 1.5T Siemens scanner during free breathing. Images were reconstructed onto 80x80x80 grids with FOV of 120mm^3 as isotropic. The xenon was dosed at 6mL/kg using a total of 750mL over a 3-minute period of imaging. Projection images were assigned to 16 bins based on timing within the respiratory cycle. Dynamic HXe MRI was utilized to assess the gas exchange efficiency and ventilation dynamics [1], providing a unique insight into the functional impacts of TIS on lung parenchyma using direct imaging of an imaging gas contrast. This innovative approach complemented our previous CT imaging data and offered a more comprehensive understanding of the respiratory mechanics and detailed regional gas exchange, which is critical for understanding the impact of thoracic deformities on pulmonary physiology.

RESULTS: An acute TIS occurred in the immediate postoperative period of the operated rabbit, requiring oxygen supplementation and slow return to room air over 24 hours. Both rabbits tolerated the anesthetic events with no adverse effects. Clinical observations in the postoperative period were that the TIS-induced rabbit had a longer recovery period at each anesthetic event, requiring supplemental O_2 for 1-2 hours longer than the control rabbit. With a gradual return to room air the rabbits saturation remained 85-100%, whereas without O_2 supplementation SpO_2 would drop below 80% and an increased respiratory rate and effort were appreciated. Coronal deformity reached a maximum Cobb angle of 45º by 20 weeks of age. Functional residual capacity (FRC) maps for each rabbit at three different age groups were compiled. In both rabbits there was position dependent atelectasis that was observed, which lowered the FRC. Moreover, increased intraregional FRC heterogeneity is observed in the tethered hemithorax of the operated rabbit (right lung) compared to all other lung fields (Fig. 1). This was observed at all timepoints. The gas exchange appears heterogeneous with both elevated and reduced regions at the upper and lower lobes of the tethered lung (red and blue arrows; Fig. 2B), and the site of maximum curvature. With HXe MRI there was a reduction of FRC at end-exhale that leads to an increase in FV (Fig. 2), contrasting the upper lung lobe which shows elevated FRC, and low FV values. The TV did not hot change substantially throughout the lung field, except for a small area at the site of maximum hemithorax collapse in the tethered animal. This bimodal nature of lung function, as depicted in histograms of the ventilation parameters (Fig. 2B) was not observed in the control animal.

DISCUSSION: The integration of hyperpolarized xenon-^{129} MRI imaging into our evaluation provided a more comprehensive understanding of the functional changes within the lungs due to TIS. These dynamic imaging techniques, particularly the use of hyperpolarized gas, offer a non-invasive window into the pulmonary pathophysiology of TIS and may be pivotal in guiding treatment decisions and evaluating surgical outcomes in pediatric patients (Fig.3).

SIGNIFICANCE/CLINICAL RELEVANCE: Development of a non-invasive modality to further characterize functional maps of respiratory mechanics will provide improved understanding of pathophysiologic changes in TIS that will aid in monitoring and development of improved interventions in affected children.

REFERENCES: [1] Hamedani H. et al. ATS. 2022

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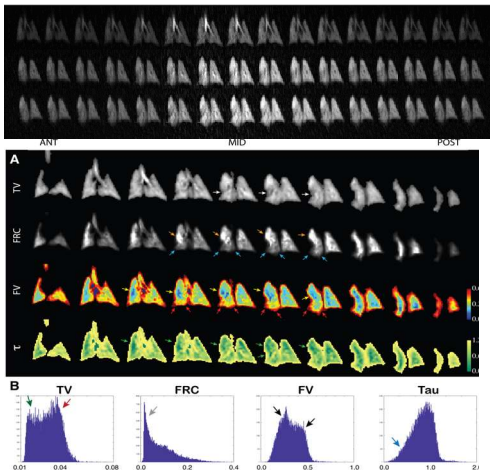

Figure 1: Raw HXe dynamic images for three representative coronal slices (from top to bottom depict anterior to posterior) in the TIS rabbit for one breathing cycle shown in 16 phases: from left to right is the end-exhale to end-inhale, returning to end-exhale.

Figure 2: Ventilation parameters for one representative slice from top to bottom are the regional TV, regional FRC, Fraction Ventilation (FV = TV/(TV+FRC)).In the right lower lobe, a reduction of FRC (at end-exhale) leads to an increase in FV (blue and red arrows). In contrast, the upper lobe shows elevated FRC (orange arrows) and low FV values (yellow arrows). Reduced TV seen in the middle of the lung at the maximum curvature (white arrows). **Fig. 2B:** Histogram graphs of ventilation parameters over respiratory cycle.

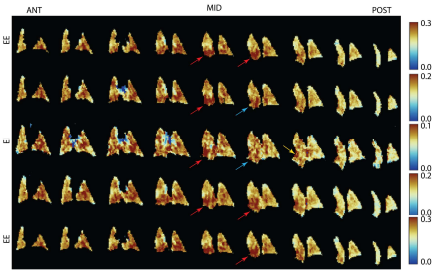

Figure 3: A dynamic map of gas exchange during breathing cycle; from top to bottom we are showing 5 out of 16 phases, with the first phase starting at end-expiratory, the middle row is end-inspiratory phase, and the final row returns to end-expiratory phase.