Three-dimensional volumetric analysis of the lung during respiration in ventilated mice

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Introduction. Volumetric analysis of lung is particularly important to understand respiratory mechanics since the biomechanical properties of the lung change in various pulmonary disorders [1]. We have previously reported that respiratory-gated dynamic MRI enabled us to monitor lung motion during breathing in a transgenic mouse model [2]. However, the study has utilized free-breathing data where the acquisition was able to be performed just at end-expiratory and end-inspiratory phases. We have recently established a novel method which enables mouse lungs to be imaged at the precise timepoint of the acquisitions within the breathing cycle by a cine-mode dynamic MRI in conjunction with a computer-controlled small animal ventilator (SAV). Clinically, controlling the positive end-expiratory pressure (PEEP) level can be used to support patients recovering from severe airway disease by preventing the collapse of small airways at the end of expiration, and thereby reducing the pressure needed to reinflate the lungs for the subsequent breath. PEEP levels are varied to induce different respiratory mechanics in a controlled fashion to simulate pathological changes in an animal. In this work, we evaluated the volumetric change of the lung during breathing by three-dimensional (3D) dynamic MRI acquired over a respiratory cycle under ventilation at different PEEP and end-inspiratory pressure levels.

Materials and Methods. Under anesthesia with 2% isoflurane, five normal mice (Balb/c) weighing 20-25 g were tracheostomized in the supine position; subsequently, the trachea was cannulated using a 20-gauge non-metallic cannula, about 1 cm long. The cannula was connected via a 1.6 m-long tube to a SAV (FlexiVent, SCIREQ, Quebec, Canada), and all animals were placed with a respiratory sensor in the 4.7 T MRI system (Biospec 47/40, Bruker BioSpin, Karlsruhe, Germany). The animals were mechanically ventilated at a frequency of 120 breaths/min (500 msec/breath) where the intrapulmonary pressure between end-expiration and inspiration was set as 10 cmH_2O. In each animal, the serial 3D MRI, which was gated using a respiratory triggering system, was repeated under controlled respiration by the ventilator at four different PEEP levels of 0, 4, 8, and 12 cmH_2O in a random order. In this setting, the lungs were inflated until the end-inspiratory pressure became 10, 14, 18, and 22 cmH_2O, respectively. FOV was set at $2.6 \times 2.6 \times 2$ cm^3 to cover the entire lung in the coronal plane and gradient echo imaging was performed in cine mode. TR was selected as 1/10 of one respiratory cycle (50 msec) to obtain the 10 serial phase images over the respiratory cycle. Other scan parameters were: matrix = $64 \times 64 \times 50$ (zerofilled to $64 \times 64 \times 64$), minimum TE (= 1.8 msec), and NEX = 1. All data were computed to generate volume rendered (VR) images using an interactive, semi-automated level-set segmentation (Fig. 1) [3] and the lung volume was calculated. Using another set of four mice, the airway resistance, which is one of the parameters of lung tissue mechanics, was measured by the same SAV at PEEP levels of 0, 4, 8, and 12 cmH_2O, in the standard procedure [4].

Results and Discussion. Fig. 2 exhibits the changes in lung volume during the inspiratory phase at different PEEP levels (N=5). The minimum lung volume at the end-expiratory phase (functional residual capacity: FRC) increased significantly as the PEEP increased. This is observed at any physiological timepoint over the respiratory cycle. The actual inflated volume (volume change between end-expiration and end-inspiration), however, decreased as the PEEP levels increase (Table 1). This result implies that the lung tissue compliance becomes higher when inflation starts from PEEP0 than from other PEEPs since compliance is derived from the slope of the pressure-volume curve. Further, the FRC demonstrated strong negative linear correlation ($R^2 = 0.98$) with the airway resistance (Fig. 3), indicating the increased extent of recruited alveoli at higher PEEP levels. In summary, our method of cine-mode 3D MR image sequence of normal mice under controlled mechanical ventilation allows us volumetric analysis of mice lungs at pre-defined phases of the complete respiratory cycle. The results showed the relationship to a mechanical property. We can design further studies for better understanding of mechanisms of respiration or pulmonary diseases using this method in small animals.

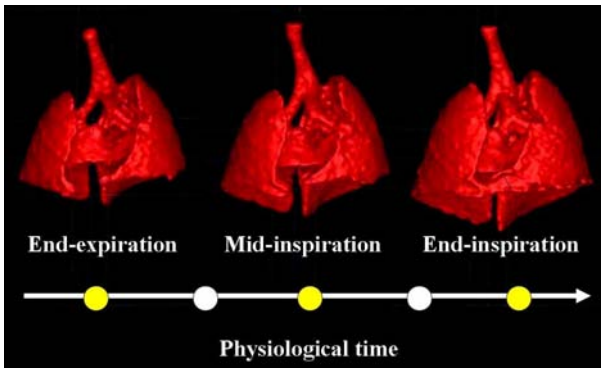

Fig. 1. 3D VR images of a ventilated mouse lung over the respiratory cycle. Three of 10 images obtained at end-expiration, mid- and end-inspiration (yellow points) were presented, demonstrating the increasing lung volume during inspiratory phase.

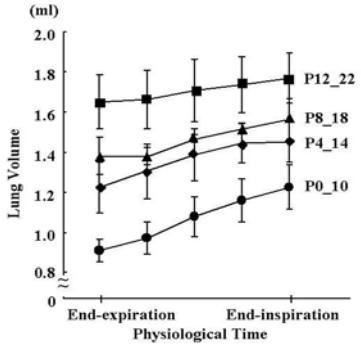

Fig. 2. Change in lung volume during the inspiratory phase at different PEEP levels (0, 4, 8, 12 cmH_2O). The end-inspiratory pressures were 10, 14, 18 and 22 cmH_2O, respectively.

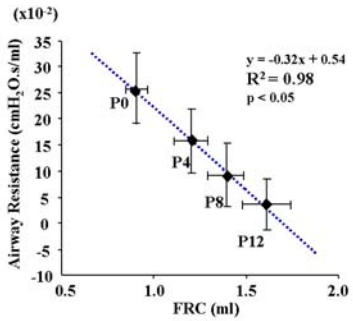

Fig. 3. Relationship between the airway resistance and functional residual capacity (FRC) with PEEPs.

Table. 1 Comparision of actual inflated volume (AIV) at four different PEEPs and limited intrapulmonary pressures

	P0_10 (cmH_2O)	P4_14 (cmH_2O)	P8_18 (cmH_2O)	P12_22 (cmH_2O)
AIV (ml)	**0.35 ± 0.06**$^{*,\#}$	**0.24 ± 0.03**$^{\$}$	**0.19 ± 0.04**	**0.14 ± 0.03**

Mean ± S.D.

*$p < 0.0001$ vs. P8 and P12, $^{\#}p < 0.01$ vs. P4, $^{\$}p < 0.001$ vs. P12 by Bonferroni test

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