Four-dimensional volumetric analysis of the lung over the respiratory cycle in ventilated mice with emphysema

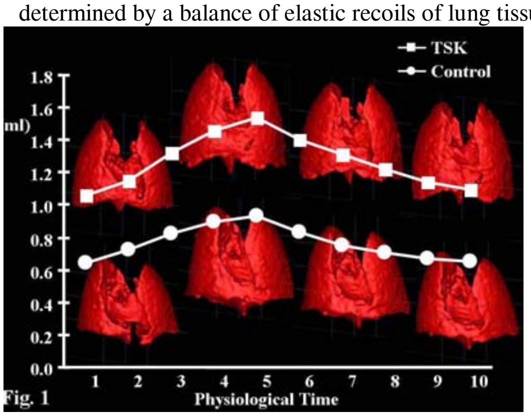
S. Kubo[1], T. A. Sundaram[2], J. C. Gee[3], H. Hatabu[4], and M. Takahashi[1]

[1]Radiology, Beth Israel Deaconess Medical Center, Boston, MA, United States, [2]Radiology, University of Pennsylvania, Pennsylvania, Philadelphia, United States, [3]Radiology, University of Pennsylvania, Philadelphia, PA, United States, [4]Radiology, Brigham and Women's Hospital, Boston, MA, United States

Introduction: Volumetric analysis of lung is particularly important to understand respiratory mechanics since the biomechanical properties of the lung change in various pulmonary disorders including chronic obstructive pulmonary disorders [1]. Although the understanding of the mechanical properties of the mammalian respiratory system and how they change under the influence of drugs and in disease are frequently pursued in small animals, the studies for the measurements of lung volume in mice are still scarce due to their small sizes. Previously, we demonstrated a new method of dynamic lung volume measurement in which mice lungs can be imaged at the precise physiologic timepoint by 4D MR microscopy in conjunction with a computer-controlled small animal ventilator (SAV) [2]. The method could detect the change of the lung distensibility over a respiratory cycle among the different positive end-expiratory pressure (PEEP) levels where changes in intrinsic biomechanics was introduced in a controlled fashion simulating pathological changes. In this work, we investigated the dynamic volumetric changes of the lung at different PEEP levels in a transgenic mice model of emphysema, tight skin (tsk) mice, which has been proposed as a genetically determined model characterized by alveolar enlargement and physiologic evidences of emphysema [1].

Materials and Methods: Under anesthesia with 2% isoflurane, five 8 week-old normal mice (Balb/c) weighing 18 ± 2 g and five 8 week-old tsk mice weighing 18 ± 2 g were tracheostomized in the supine position; subsequently, the trachea was cannulated using a 20-gauge non-metallic cannula, about 1 cm long. Then, the cannula was connected via a 1.6 m-long tube to a SAV (FlexiVent, SCIREQ, Quebec, Canada), and these animals were placed with a respiratory sensor in the 4.7 T MRI system (Biospec 47/40, Bruker BioSpin, Karlsruhe, Germany). In each animal, the 4D MR microscopy was conducted twice at different levels of PEEP 0 and 4 cmH_2O in a random order where the end-inspiratory pressure levels were set at 10 and 14 cmH_2O (P0_10, P4_14, respectively), so that the difference in intrapulmonary pressure between end-expiration and end-inspiration was consistent as 10 cmH_2O. FOV was set at $2.6 \times 2.6 \times 2$ cm^3 to cover entire lung in the coronal plane and a 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 3D MR images over the respiratory cycle. Other scan parameters were: matrix = 64 × 64 × 50 (zerofilled to 64 × 64 × 64), minimum TE (= 1.8 msec), and NEX = 1. To calculate the dynamic lung volume, all data were computed to generate volume rendered (VR) images in each image frame (F1-F10, Fig. 1) using an interactive, semi-automated level-set segmentation based on a finite snake algorithm (Insight SNAP) [3]. After scanning, all mice lungs were histologically examined.

Results and Discussion: The mean end-inspiratory volume (EIV) was significantly larger in the tsk group than that in the control group at both P0_10 (1.66 ± 0.42 ml vs. 0.90 ± 0.11 ml, p= 0.004) and P4_14 (1.06 ± 0.20 vs. 2.02 ± 0.30 ml, p= 0.0003) respectively (Fig. 2). The mean end-expiratory volume (EEV) was significantly larger in the tsk group than that in the control group at both P0_10 (1.20 ± 0.32 vs. 0.59 ± 0.07 ml, p= 0.003) and P4_14 (0.79 ± 0.14 vs. 1.72 ± 0.27 ml, p= 0.0001). The mean actual inflated volume (AIV) between the end-expiratory and inspiratory phases as well as the respiratory compliance, calculated as the total AIV (AIV_{F1F5}) divided by 10 cmH_2O, were significantly larger in the tsk group than those in the control group at P0_10, whereas no significance was found between the groups at P4_14 (Table 1). On inspiration at P0_10 (Table 2), the control group demonstrated that %change in lung volumes relative to the total AIV was smaller at the early phase (phase 1→2), then increased at the middle phases (2→3 and 3→4) and leveled off at the late phase (4→5). The result might be consistent with a fact, when the lung is inflated, that the fibers in the alveolar walls and around the blood vessels and bronchi are stretched or distorted, so they have a tendency to return to their original shape and therefore develop elastic recoil where more pressure is needed to reinflate from the collapsed state at end-expiration. This trend became blurred in the tsk group at same PEEP level, implying that alveolar collapse might have reduced in emphysematous lung. At PEEP4 which prevents the collapse of alveoli and small airways to make the intrinsic tissue compliance to be highest at the end-expiration [2], the early lung inflation increased and the difference between the groups disappeared. The reducing %change at the later inspiratory phases must have been determined by a balance of elastic recoils of lung tissue as well as different muscles of respiration such as chest wall.



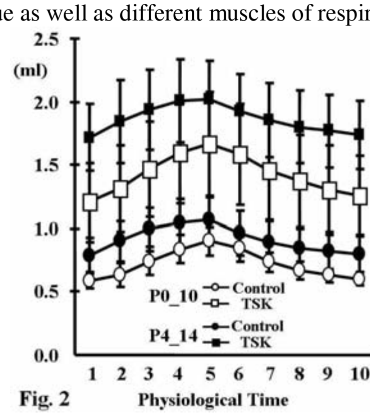


Fig. 1. 3D VR images of a ventilated control and tsk mice lung over the respiratory cycle.

Fig. 2. Change in lung volume in control and tsk mice over the respiratory cycle at P0_10 and P4_14.

Table 1. Comparison of AIV and compliance between control and tsk groups at P0_10 and P4_14

AIV (ml)	Control	tsk	p-value
P0_10	0.31 ± 0.08	0.46 ± 0.11	0.04
P4_14	0.27 ± 0.06	0.28 ± 0.05	0.77
Compliance (ml/cmH_2O x10^{-3})	Control	tsk	p-value
P0_10	31 ± 8	46 ± 11	0.04
P4_14	27 ± 6	28 ± 5	0.77

Mean ± S.D. AIV: actual inflated volume By Unpaired t test

Table 2. Change in lung volumes between serial inspiratory phases

	P0_10			P4_14		
Inspiration	Control	tsk	p-value	Control	tsk	p-value
AIV_{F1F2}/AIV_{F1F5} x100 (%)	7 ± 8	29 ± 23	0.09	41 ± 9	41 ± 28	0.99
AIV_{F2F3}/AIV_{F1F5} x100 (%)	41 ± 8	39 ± 12	0.67	34 ± 2	34 ± 12	0.97
AIV_{F3F4}/AIV_{F1F5} x100 (%)	46 ± 12	30 ± 9	0.04	21 ± 2	24 ± 6	0.29
AIV_{F4F5}/AIV_{F1F5} x100 (%)	31 ± 8	12 ± 12	0.01	7 ± 5	7 ± 15	0.17

Mean ± S.D. AIV; actual inflated volume, By Unpaired t test

References

1. Vieillard-Baron A et al., Eur Respir J Suppl. 42:43s (2003).
2. Kubo S et al., 14th ISMRM Annual Meeting, Seattle, USA (2006).
3. Szapiel S. V., et al., Am Rev Respir Dis.;123:680 (1981).