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Localized morphometric deformations of small airways and alveoli in intact mouse lungs under quasi-static inflation

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Abstract

Localized morphometric deformations of small airways and alveoli during respiration have several biomechanical and physiological implications. We developed fast synchrotron radiation CT system to visualize the small airways and alveoli of an intact mouse lung without fixation and dehydration, and analyzed their localized morphometric deformations between functional residual capacity (FRC) and total lung capacity (TLC). The maximum resolution of 32.6 lp/mm at the 5% modulation transfer function level can be achieved with 11.8-μm voxels and 7-min scanning. Compared with the values at FRC, the diameter and length for smaller airways (diameter at FRC <200 μm) increased by 68.8% and 29.5% (averaged value), and those for larger airways (diameter at FRC >400 μm) increased by 45.2 and 22.9% (averaged value), at TLC. Moreover we defined the volume behavior as the percentage of airway volume at FRC for TLC. The volume behavior for the small airways was not similar to that of the lung volume. These results indicated that all airways did not behave homogenously.

Keywords: Three-dimensional visualization; Fast synchrotron radiation CT; Lung compliance; Heterogeneity

1. Introduction

Airway consists of a number of various compliant tubes from trachea to alveolus, and the airway geometry deforms dramatically during respiration. The overall airway deformations are closely related to bulk lung compliance, which are dominated by tissue elasticity and surface tension. Respiratory diseases, however, occur most frequently at small airways and alveoli (Wright, 2002; Tashkin, 2002), and the condition of small airways and alveoli has important physiological and clinical implications. In many respiratory diseases, significant compliance abnormalities mainly occur in localized regions of bronchi and bronchioles, and thus in addition to the overall airway deformations, the localized, or the microscopic deformations of both parenchyma and small bronchi or bronchioles based on small-scale observations must be identified.

In the previous works, three methods were reported to evaluate the localized airway deformations. One

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approach is to fix and visualize lungs at several pressures by using optical microscopy (Klingele and Staub, 1971; Okazawa et al., 2000). The dehydrated and fixed preparations have been used to analyze the 3D structure of small airways and alveoli in detail. Hammersley and Olson (1992) investigated the geometry of small airways of humans using the cast model technique. Kriete et al. (2001) sliced the fixed lungs of rats and mice into 70-μm thick sections and visualized the alveolus using a confocal laser scan microscope and micro-CT. However, small airways are flexible tissues, and therefore their geometry varies markedly during respiration (Naureckas et al., 1994). Moreover, these fixed preparation lead to a significant loss of airway compliance as well as a deformation of the microscopic lesions of the lung tissue. Another approach is to apply bronchography (Hughes et al., 1972; Menkes et al., 1972; Sittipong and Hyatt, 1974). They insufflated tantalum powder into a lung as a contrast agent and then used bronchograms to analyze the changes in the diameter and length of the individual bronchial segments at various transmural pressures. However, these measurements were limited to large bronchi, over 0.5 mm in diameter. The other approach is to measure the mechanical properties in vitro. Tiddens et al. (1999) measured the mechanical properties of excised small airway segments in vitro. However, in situ, the intrapulmonary airways are surrounded by lung parenchyma and thorax, and the effective microscopic airway compliance is influenced by the surrounding support (Fig. 1). Hyatt and Flath (1966) and Takishima et al. (1975) measured diameter and length behavior of large airways (diameter: over 1 mm) and reported that intrapulmonary airways are stiffer than the excised airways. Recently, Sera et al. (2003b) proposed a novel technique to visualize small airways of the excised rat lungs without dehydration and fixation. They visualized the small airways (diameter: over 150 μm) in detail by staining the lung tissue with a radiopaque solution and by imaging with micro-CT. Using this technique, they analyzed the localized deformation based on the microscopic regions of airway segments (Sera et al., 2004). However, the radiopaque solution probably permeated into the lung tissue by pinocytosis and through the disturbed tight-junctions (Haller et al., 1997; Schick and Haller, 1999), and might leak into alveolus.

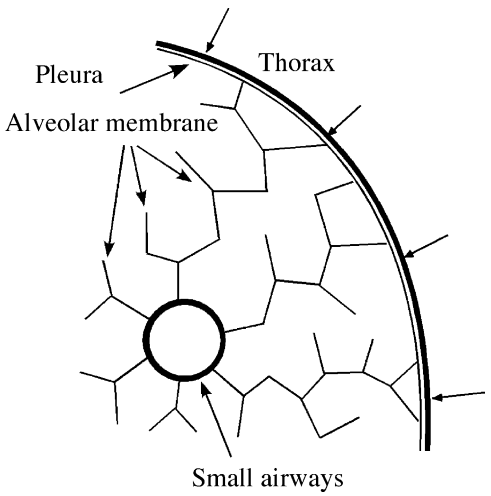

Fig. 1. The schematic model of small airways and alveoli in thorax.

The localized deformations reflect the restricted regions in which small airways were embedded into the parenchyma and thorax. In this study, we hypothesized that small airways in intact lung were stiffened in parenchyma and thorax. We determined the localized morphometric deformations based on microscopic regions of airways, such as small airways and alveoli, during respiration (diameter, length and airway volume behavior) to establish their mechanical properties. The measurements can be potentially used as physiological and clinical indices.

In this study, we developed the “fast” synchrotron radiation CT system to visualize the small airways and alveoli of intact mouse lung. Synchrotron radiation gives a much higher flux and collimated X-ray beam than a laboratory microfocal X-ray source. Recently, the solid preparations (fixed lung, Ikura et al., 2004), bone (Ito et al., 2003) and coronary arteries (Toyota et al., 2002) were visualized in detail using synchrotron radiation CT. If the samples are not dehydrated and fixed, they deform during the CT scan time (generally, several hours). To visualize small airways and alveoli of intact mouse lung, the scan time had to be reduced to prevent motion artifacts (less than 15 min). Further, to evaluate the localized morphometric deformation of small airways and alveoli, we visualized the same airways of the same lung at functional residual capacity (FRC) and total lung capacity (TLC) under quasi-static inflation process. Our results show that not all airways deform in the same manner. In particular, the diameter behavior was higher for smaller airways, and the percentage of airway volume for the small airways was