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● *Original Contribution*

# ULTRASOUND STRAIN MEASUREMENTS FOR EVALUATING LOCAL PULMONARY VENTILATION

JONATHAN M. RUBIN,* JEFFREY C. HOROWITZ,* THOMAS H. SISSON,* KANG KIM,† LUIS A. ORTIZ,† and JAMES D. HAMILTON‡

*University of Michigan, Ann Arbor, Michigan, USA; †University of Pittsburgh, Pittsburgh, Pennsylvania, USA; and ‡Epsilon Imaging Inc., Ann Arbor, Michigan, USA

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**Abstract—Local lung function is difficult to evaluate, because most lung function estimates are either global in nature (*e.g.*, pulmonary function tests) or require equipment that cannot be used at a patient's bedside, such as computed tomography. Yet, local function measurements would be highly desirable for many reasons. Recently, we were able to track displacements of the lung surface during breathing. We have now extended these results to measuring lung strains during respiration as a means of assessing local lung ventilation. We studied two human volunteers and 14 mice with either normal lung function or experimentally induced pulmonary fibrosis. The differences in strains between the control, normal mice and those with pulmonary fibrosis were significant ($p < 0.0001$), whereas the strains measured in the human volunteers closely matched linear strains predicted from the literature. It may be possible to use ultrasonography to assess local lung ventilation in a clinical setting. (E-mail: Jrubin@umich.ed)** © 2016 Published by Elsevier Inc. on behalf of World Federation for Ultrasound in Medicine & Biology.

***Key Words:*** **Ultrasound strain measurement, Lung ventilation, Lung ventilator monitoring, Pulmonary fibrosis, Lung ultrasound, Chronic obstructive pulmonary disease, Acute respiratory distress syndrome.**

## INTRODUCTION

Many lung diseases are patchy or non-uniform in their distributions. Yet, these non-uniformly distributed lung diseases, such as idiopathic pulmonary fibrosis and acute lung injury/acute respiratory distress syndrome, are still often evaluated using methods that provide only generalized assessments of lung function (Raghu et al. 2011; Thille et al. 2013; Victorino et al. 2004). For example, idiopathic pulmonary fibrosis evaluation involves pulmonary function studies, which are global estimates of lung function that cannot assess the true distribution of the disease (King et al. 2014; Oldham and Noth 2014; Raghu et al. 2011, 2012).

Local assessments can be performed; the most common is the standard chest radiograph. However, because of the limitations of chest radiographs, regional evaluations of diseases with non-uniform lung involvement generally use computed tomography (CT), with CT generally considered the gold standard for local lung architecture (Lynch et al. 2005). Yet, CT is not perfect. CT is not a portable technique, so it cannot be used to assess lung function or mechanics in remote locations such as in intensive care units (ICU), and it is not optimal for screening/monitoring because of the radiation risk. Further, CT does not provide much functional information without extensive computational efforts (Galban et al. 2012).

Magnetic resonance imaging (MRI) is another option with the potential to measure local lung ventilation/function, and new developments in parallel imaging, shared echo techniques and rotating phase encoding are making the method more viable (Puderbach et al. 2007). However the technique has significant problems with signal to noise because of the low proton densities in the lungs, susceptibility artifacts, the inherent qualitative nature of the imaging itself and the inability to conduct lung assessments at clinical care sites such as in intensive care units (Puderbach et al. 2007).

The best present option for a monitoring technique for local pulmonary function/disease is electrical impedance tomography (EIT). EIT reconstructs local estimates of pulmonary impedance, which correlate to the degree of

Address correspondence to: Jonathan M. Rubin, Department of Radiology, University of Michigan Hospitals, 1500 East Medical Center Drive, Ann Arbor, MI 48109, USA. E-mail: Jrubin@umich.ed

local aeration of lung. However, EIT has several limitations: (i) it is restricted to one transverse plane through the chest; (ii) it would be a difficult monitoring mode because the chest needs to be wrapped in detectors for a measurement; (iii) presently the impedance estimates do not seem to correlate with CT lung density; and (iv) the results are qualitative, so only relative changes can be evaluated (Victorino et al. 2004).

There is now a great deal of interest in ultrasound imaging for evaluation of lung disease. Many articles illustrating the utility of ultrasonography in diagnosing and assessing various pulmonary and intrathoracic diseases have been published (Dietrich et al. 2003). In addition to standard applications such as localization of pleural effusions, physicians are now using ultrasound to identify and characterize such conditions as pulmonary edema, pulmonary fibrosis and pneumonias (Agricola et al. 2005; Lichtenstein et al. 2004; Mathis et al. 1992; Tardella et al. 2012). Almost all of these evaluations have been based on characterization of artifacts that likely occur between the pleura and lung surface. These typically manifest as linear artifacts that project from the lung surface into what would be gas-filled lung. The assessment of the underlying conditions based on the number and quality of these artifacts is qualitative or semi-quantitative at best, and none of them assess any component of lung physiology or mechanics (Soldati et al. 2011).

There is now evidence that local lung strain can be estimated with ultrasound. Measuring lung strain could provide a method of monitoring local lung ventilation changes that produce these strains. In a recent publication, we reported that we could track the motion of the lung surface using ultrasound 2-D speckle tracking (Rubin et al. 2012). The purpose of this tracking was to estimate tissue displacements for guiding radiation therapy treatments of tumors, and as such, we also tracked the motion of normal liver, a liver with an hepatocellular carcinoma and prostate motion that we artificially induced by moving the transducer. In this article, we use the displacement estimates on the lung surface to calculate the local strains produced by the expansion and contraction of the lung during breathing in human volunteers and in a murine model of acute lung injury and pulmonary fibrosis. As would be expected, during inspiration, strain increases, and during expiration, strain decreases. This measurement could lead to an entirely new application of ultrasound to pulmonary disease.

## METHODS

### *Mouse scans*

To assess the ability of ultrasound strain measurement to evaluate pulmonary function, we targeted a mouse model of pulmonary fibrosis for analysis.

Fourteen C57BL/6 mice were included in the experiment. The mice were weight- and age-matched (18–22 g at 6–8 wk of age). To produce pulmonary fibrosis, six mice were administered bleomycin intratracheally (1.2 U/kg in 50 $\mu$L of sterile phosphate-buffered saline), as previously described (Courey et al. 2011). Eight control mice were injected for the same duration with 50 $\mu$L of phosphate-buffered saline alone. The scans were performed 21 d after the injections to ensure sufficient time for pulmonary fibrosis to develop in the bleomycin-injected mice. All protocols used in this study were approved by the University of Michigan Unit for Laboratory Animal Medicine.

The mice were scanned in the prone position. Hair was removed from bilateral chest walls. The animals were anesthetized with xylazine (5–10 mg/kg injected intraperitoneally) and ketamine (80–120 mg/kg injected intraperitoneally). We imaged the lungs with a commercially available ultrasound scanner (Vevo 2100, FujiFilm VisualSonics, Toronto, ON, Canada) using a 55-MHz linear array. The transducer was held in position against each mouse's chest using a restraining device provided by the manufacturer. B-Mode cine loops of respiratory motion were captured in transverse and sagittal orientations, although only the sagittal motions were evaluated in this study. Data were stored in either Digital Imaging and Communications in Medicine (DICOM) format or radiofrequency (RF) format. RF data were subsequently converted into B-mode gray-scale loops for tracking. The loops were on the order of 0.5–1 s long and were sampled at around 300–400 frames/s depending on such parameters as image depth, image width and beam density.

The imaging loops were then transferred to a work station where commercially available speckle tracking software (EchoInsight, Epsilon Imaging, Ann Arbor, MI, USA) was used for analysis. The loops were evaluated interactively where a region of interest (ROI) pair (*i.e.*, two connected ROIs) was placed along the moving lung surface, which was easy to identify based on its motion on the real-time loops (Fig. 1). ROI motion was tracked in two dimensions (laterally and axially). Tissue displacements were estimated based on the regional 2-D cross-correlation of the gray-scale signal between frames. Lung surface strain was determined primarily by lateral motion due to acquisition geometry, which is orthogonal to the standard axial strains measured in most 1-D applications (Ophir et al. 1991).

Strain was defined as the Lagrangian strain estimated from two user-defined regions of interest selected on the lung surface. Strain $= (L_f - L_i)/L_i$, where $L_f$ is the time varying distance between the centers of the ROI pair, and $L_i$ is the initial distance between the centers of the ROI pair. The continually changing strain values