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● *Original Contribution*

CHARACTERIZATION OF THE LUNG PARENCHYMA USING ULTRASOUND MULTIPLE SCATTERING

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Abstract—The purpose of the study described here was to showcase the application of ultrasound to quantitative characterization of the micro-architecture of the lung parenchyma to predict the extent of pulmonary edema. The lung parenchyma is a highly complex and diffusive medium for which ultrasound techniques have remained qualitative. The approach presented here is based on ultrasound multiple scattering and exploits the complexity of ultrasound propagation in the lung structure. The experimental setup consisted of a linear transducer array with an 8-MHz central frequency placed in contact with the lung surface. The diffusion constant D and transport mean free path L^* of the lung parenchyma were estimated by separating the incoherent and coherent intensities in the near field and measuring the growth of the incoherent diffusive halo over time. Significant differences were observed between the L^* values obtained in healthy and edematous rat lungs *in vivo*. In the control rat lung, L^* was found to be 332 μm (±48.8 μm), whereas in the edematous lung, it was 1040 μm (±90 μm). The reproducibility of the measurements of L^* and D was tested *in vivo* and in phantoms made of melamine sponge with varying air volume fractions. Two-dimensional finite difference time domain numerical simulations were carried out on rabbit lung histology images with varying degrees of lung collapse. Significant correlations were observed between air volume fraction and L^* in simulation ($r = -0.9542, p < 0.0117$) and sponge phantom ($r = -0.9932, p < 0.0068$) experiments. *Ex vivo* measurements of a rat lung in which edema was simulated by adding phosphate-buffered saline revealed a linear relationship between the fluid volume fraction and L^*. These results illustrate the potential of methods based on ultrasound multiple scattering for the quantitative characterization of the lung parenchyma. (E-mail: kmohant@ncsu.edu) **© 2017 World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Quantitative ultrasound, Multiple scattering, Lung parenchyma, Interstitial syndrome, Edema, Fibrosis.**

INTRODUCTION

Ultrasonic quantitative characterization of the lung parenchyma has remained elusive because of the presence of air-filled alveoli and the very complex micro-architecture of the lung tissue. These specific properties of the lung tissue are responsible for ultrasound multiple scattering, a regime in which the waves do not propagate straight and in which the linear relationship between propagation time and propagation distance is lost, altering conventional ultrasound imaging. We propose a method in which we exploit ultrasound multiple scattering by the alveoli to quantitatively characterize the lung parenchyma. Indeed, each scattering event can be seen as an opportunity for the wave to embed information on the micro-architecture of the parenchyma. Multiple scattering is becoming a widely studied phenomenon and has been proven useful in the characterization of disordered media, exploiting coherent and incoherent effects in classical, electromagnetic or acoustic waves (Sheng 2006; Tourin et al. 2000).

Conventional lung imaging is generally done using chest radiography (CXR) or thoracic computed tomography (Rubinowitz et al. 2007). Both these imaging modalities have limitations, which places constraints on their applicability. CXR is constrained by limited diagnostic performance, portability of bedside radiography and X-ray exposure issues. Because of the moving thorax, the spatial resolution decreases and leads to poor-quality X-ray films with low sensitivity. X-ray beam

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origination is not tangential to the diaphragmatic cupola, hindering correct interpretation of the thoracic structures (Bekemeyer et al. 1985; Henschke et al. 1997). Although thoracic computed tomography is the gold standard for lung imaging, it is very costly, and transportation of the critically ill to the concerned department combined with radiation exposure increases the measurable risk.

Over time, the use of lung ultrasound in patients in intensive care units has gained popularity. It has been found to have higher diagnostic accuracy compared with CXR for pleural effusion and consolidation (Lichtenstein 2016; Lichtenstein and Mezière 2008). Lung ultrasound has also garnered wide applicability in the detection of pulmonary manifestations of neonatal respiratory distress syndrome (El-Malah et al. 2015). Lung ultrasound is arguably the fastest and most effective method for detecting diaphragmatic paralysis and diagnosing pleural effusion, especially when trying to differentiate between effusion and consolidation (Doerschug and Schmidt 2013). Because it is portable and has no irradiation effects, lung ultrasound has become an option for thoracic imaging in the critically ill. The conventional approach in lung ultrasound is based on the identification of 10 standardized signs: bat sign (pleural line); lung sliding (yielding seashore sign); A-line (horizontal artifact); quad and sinusoid signs, indicating pleural effusion; fractal and tissue-like signs, indicating lung consolidation; B-line and lung rockets, indicating interstitial syndrome; abolished lung sliding with the stratosphere sign, suggesting pneumothorax; and the lung point, indicating pneumothorax (Lichtenstein 2016). However, reading and interpreting these signs is subjective and operator dependent. Lung ultrasound imaging beyond the pleural layer is highly inaccurate because of the presence of multiple scattering in the parenchyma caused by drastic changes in impedance from tissue to air in the alveoli. During lung imaging, the backscattered signals are distorted, leading to artifacts and introducing large errors in reading and interpretation of the images (Lichtenstein and Mauriat 2012).

In highly complex media, the backscattered ultrasonic signals can be processed, not for imaging, but to extract quantitative parameters of the microarchitecture. Tourin et al. (2000) reported that it is possible to characterize a highly diffusive medium using parameters such as the diffusion constant (D) and various mean free paths. These were assessed in complex media made of steel rods acting as scatterers. Using ultrasound multiple scattering has also proved advantageous in providing a quantitative spatial estimate for complex bone architectures, porosities and spatial densities. Aubry et al. (2008) used multiple scattering successfully to make local measurements in the human trabecular bone, which is highly complex and diffusive in nature. The approach they developed was successfully tested on a phantom consisting of steel rods distributed in water (Aubry and Derode 2007). The diffusion constant, as illustrated in this article, is relevant to the assessment of lung edema and air volume fraction in the lung. We report, for the first time, that ultrasound multiple scattering, usually considered an obstacle to imaging of highly scattering media, can be taken advantage of in characterizing the lung parenchyma.

Because of the very strong impedance difference between the lung tissue and the alveoli, it is assumed that the tissue acts as the propagating medium, whereas the alveoli play the role of scatterers. As reported in earlier studies, the lung parenchyma can be treated as a sponge whose volume fraction varies during inhaling and exhaling. Numerous studies have been performed with ultrasound as well as magnetic resonance imaging using gelatin sponges as a lung-mimicking phantom (Molinari et al. 2014; Spinelli et al. 2012). Spinelli et al. used a gelatin sponge as a simplified structure of the lung to reproduce its viscoelastic properties and generate a simplified model, which can be used to reproduce mechanical, architectural and acoustic properties of pulmonary tissues. Earlier models developed from culture of pulmonary epithelial cells were complex and were identified as a major challenge (Spinelli et al. 2012).

In this study, we proposed taking advantage of the complexity of the ultrasonic signals and of the high diffusivity of the lung parenchyma to characterize the lung using wave transport parameters, namely, the diffusion constant D and the transport mean free path L^* (Tourin et al. 2000). These parameters are estimated by processing the ultrasonic signals backscattered from the lung after a pulse transmission with an 8-MHz central frequency. We provide a quantitative estimate of these transport parameters in simulations, sponge phantoms and the rat lung *ex vivo*, *in vivo* and in models of pulmonary edema.

METHODS

Ultrasound experimental setup

In both simulations and experiments, ultrasound pulses were transmitted using single elements of a linear transducer array, one by one. For all numerical simulations, a 64-element linear array with a central frequency of 8 MHz was simulated. For all experiments, we used a 128-element Verasonics L11-4v linear array connected to a Verasonics Vantage ultrasound scanner (Verasonics, Kirkland, WA, USA). The transducer was coupled to the lung by a layer of ultrasound coupling gel (approximately 5 mm). In both simulations and experiments, all of the elements of the array were fired one by one, transmitting a 2-cycle pulse with a central frequency of 8 MHz into the medium. For each transmitted pulse, the

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