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Imaging regional lung function: A critical tool for developing inhaled antimicrobial therapies☆

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ABSTRACT

Alterations in regional lung function due to respiratory infection have a significant effect on the deposition of inhaled treatments. This has consequences for treatment effectiveness and hence recovery of lung function. In order to advance our understanding of respiratory infection and inhaled treatment delivery, we must develop imaging techniques that can provide regional functional measurements of the lung.

In this review, we explore the role of functional imaging for the assessment of respiratory infection and development of inhaled treatments. We describe established and emerging functional lung imaging methods. The effect of infection on lung function is described, and the link between regional disease, function, and inhaled treatments is discussed. The potential for lung function imaging to provide unique insights into the functional consequences of infection, and its treatment, is also discussed.

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1. Introduction

Respiratory infection has a profound effect on lung function. Subsequently, altered lung function has a significant impact on the delivery of inhaled treatments. Our ability to understand and treat respiratory infection would be greatly enhanced by the ability to consider the regional functional consequences of respiratory infection, and how this

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may affect inhaled treatment delivery. Lung function has traditionally been assessed using spirometry; by measuring the flow of gas at the mouth, the function of the lungs as a whole is calculated. However, the effects of disease on lung function are predominantly restricted to local regions within the lung, providing motivation for the development of imaging methods capable of providing regional lung function measurements. Functional lung imaging has the potential to address unanswered questions of lung pathophysiology [1], and to provide new insight into the development of inhaled treatments of lung disease [2].

In this review we establish the benefit of functional lung imaging in the assessment and treatment of respiratory infection. The main focus is to describe established and emerging functional lung imaging methods, with specific focus on those that may be used in lung function measurement in respiratory tract infection and for development and assessment of inhaled treatments. Table 1 summarizes the different techniques discussed, including advantages and limitations of each. The effect of infection on lung function is described, and the link between regional disease, function, and inhaled treatments is discussed. The potential for lung function imaging to provide unique insights into the functional consequences of infection, and its treatment, is also discussed.

1.1. Lung function in infection and disease

Breathing is a mechanical process where the respiratory muscles work together to produce driving pressures to expand and draw air into the lung for gas exchange [3]. The flow of air inside the lungs, and hence the regional ventilation and function, is determined by mechanical properties, most notably the resistance and compliance. The driving pressure across the respiratory system needs to overcome the total pulmonary resistance against the flow, the static elastic recoil of the alveolar tissue and the thoracic cage against the increasing volume, and also the inertial force of the gas motion.

Fig. 1 shows the basic anatomical elements of the lungs. During inspiration, the dome-shaped diaphragm contracts and flattens, enlarging the thoracic cavity resulting in a decrease of both the pleural pressure and the alveolar pressure inside the lung. This establishes a positive pressure gradient along the airway tree causing airflow into the lung. During expiration, the diaphragm relaxes, and gas is expelled from the lung due to elastic recoil of the lung tissue and chest wall.

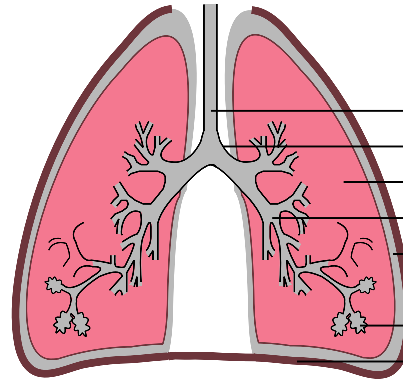

Fig. 1. Basic anatomical elements of the lungs. During inspiration, the diaphragm contracts and flattens, enlarging the thoracic cavity resulting in a decrease in pressure in the pleural cavity. This in turn expands the lungs, reducing pressure in the alveoli causing gas to be drawn in through the trachea and conducting airways.

The lung contains structures that cover a range of scales in order to deliver air to a large surface area for gas exchange [4]. The airways exhibit a branching geometry in which elements are interdependent [5]. Emergent behavior and internal feedback mechanisms mean that while local effects must be resolved, the entire respiratory system must be interrogated as a whole, and the response of isolated tissue may not easily predict whole organ response, for example when airways are constricted in asthma [6–10]. Imaging is well placed to deliver this detailed, yet holistic view of lung function *in situ*.

Disease and infection alter the mechanical properties within the lung, leading to regional alterations in lung function. For example, pulmonary fibrosis will alter the compliance of the lung parenchyma, leading to regional alterations in tissue expansion, even in the very early stages of the disease [11]. Asthma results from airway hyperresponsiveness. Exacerbations occur whereby the airways constrict and narrow, causing an increase in airway resistance that can lead to difficulty breathing and regional ventilation defects [5,6,8,12–14]. Inflammation associated with chronic obstructive pulmonary disease (COPD) leads to the destruction of elastin, which reduces lung elasticity. This results in less elastic recoil (increased compliance) reducing the ability to empty the lungs, and decreasing peak expiratory flow [15].

Table 1
Established and emerging lung imaging methods.

Section	Modality	Advantages	Limitations
Established methods			
2.1	Computed tomography	High spatial resolution	High radiation dose Limited functional information No dynamic information
2.2	4DCT registration-based ventilation	Regional functional measurement High spatial resolution	Very high radiation dose
2.3	Hyperpolarized MRI	Regional functional measurement Zero radiation dose	High cost Lower resolution Limited availability
2.4	Electrical impedance tomography	Bedside imaging High temporal resolution Regional functional measurement Zero radiation dose	Very low resolution
2.5	Nuclear Imaging methods	Regional functional measurement Deposition measurement	Poor temporal resolution High cost Logistically challenging contrast agent required
Emerging functional imaging			
3.2	Grating interferometry	Very sensitive to changes in lung structure	Very poor temporal resolution Challenging imaging setup
3.3	Propagation-based phase contrast imaging	Simple to implement Dynamic imaging High contrast within lung tissue	Less sensitive to phase contrast Requires highly coherent X-rays
3.4	Functional lung imaging using phase contrast	Regional functional measurement Dynamic information	Currently requires highly coherent X-rays
3.5	Laboratory PBI	Improved access for researchers	Under development