The Comprehensive Imaging-Based Analysis of the Lung:

A Forum for Team Science[1]

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Fundamentally important to the future of pulmonary medicine is a better description and understanding of the human lung and its response to disease, injury, and treatment, which is not based on global measures but upon quantifiable regional features. There is rapidly growing awareness for the need to volumetrically image the lung and to provide objective, quantitative measures characterizing regional lung pathology. This editorial is written by our multidisciplinary team with the goal of encouraging the imaging community to continue its strong efforts toward addressing the open issues related to lung imaging and image analysis. In addition, we would like to thank *Academic Radiology* for providing a cross-roads where clinical practice, imaging physics, physiology, biomedical engineering, and image processing can interact as we seek to better understand pathologic processes and to establish sensitive and specific endpoints for the rapid evaluation of therapeutic interventions to lung disease.

Over the past 2 years there has been a strong increase in the appearance of basic and clinical science papers in the field of lung imaging in the areas of both computed tomography (CT) (1–15) and magnetic resonance (16–21) in this journal. There has been a growing focus in the area of nodule detection (4–8), and there is a new effort to map multiple lung volumes together (9,10) for purposes of evaluating regional lung mechanics, tracking pathology over time, or comparing an individual to an image-based normative atlas (1). Methods to quantify regional lung disease are needed because the use of global measures, which do not adequately capture lung complexity and may be only minimally altered by significant local disease, not only foments an incomplete understanding of lung pathophysiology but also results in the need to study large numbers of subjects over long time periods of time to evaluate new treatments. Image-based measures, including evaluation of static and dynamic structure and function, are now recognized as very sensitive indicators of localized subclinical disease and appear to describe these complex lung processes much better. Small changes are easily detected and quantified, particularly using computer-aided analysis, resulting in a more rapid and more objective assessment of disease progression and hence therapeutic outcomes. This will obviously have important consequences for the development of therapeutic trials and shorten the road to market of novel inhaled drugs.

Currently, x-ray CT remains the imaging modality of choice for comprehensive evaluation of the lung, due in large part to the significant advances made in both temporal and spatial resolution. Multidetector-row CT (MDCT) scanners are now capable of sub–half-second data acquisition (330 msec per rotation and faster), allowing for the imaging of not only anatomy but also ventilation and perfusion, providing unprecedented structure-to-function correlations. With the rapid

Acad Radiol 2004; 11:1370–1380

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doi:10.1016/j.acra.2004.09.005

widening of the cone beam on these scanners and through the addition of more detector rows, true volumetric imaging is imminent. Over the last 5 years, many advances have been made in both image methods as well as image analysis, including tools for CT image segmentation, registration across changing lung volumes and between subjects, 3-dimensional textural analysis, and high-resolution ventilation, and perfusion measurement; these techniques have already been applied in both animal models and human subjects. However, at the same time, the growing concern over patient safety and the increasing propensity of public policy to mandate limits on the use of ionizing radiation threatens to limit full deployment of these newly emerging quantitative CT tools for comprehensive assessment of detailed lung structure-function relationships in the early detection of pathology, the temporal evaluation of disease progression, and in the evaluation of successful therapeutic interventions. Fortunately, new technological methods are emerging that allow for significant dose reduction in CT imaging of the lung. The refinement and evaluation of these low dose methods, therefore, constitute a need for enhanced efforts in new approaches to dose reduction. As dose is reduced, the accuracy of quantitative measures based on the resultant images must not be diminished. Structural detail as well as reconstructed attenuation coefficients must remain true to underlying structure and function.

As CT has rapidly advanced, the past 4–5 years have also been marked by the emergence of a new set of tools for magnetic resonance imaging (MRI) evaluation of the lung (16–21), an organ previously poorly visualized by MRI because of its low proton density and inherent air-soft tissue interface field inhomogeneity. Novel techniques for proton imaging in the presence of high concentrations of oxygen have been used to image lung structure and to measure regional lung volume, while ultra-fast imaging techniques with contrast have allowed for quantified perfusion studies. Advances in hyperpolarized gas imaging (He and Xe) have allowed for the regional assessment of peripheral airspace size using the apparent diffusion coefficients, as well as indices of regional ventilation (V), perfusion (Q), V/Q relationships, and regional oxygen concentrations. Because of the advantages of MRI in terms of radiation exposure, volumetric imaging, and temporal resolution, there is a clear need to quantitate and validate these novel MRI measures against gold standards which, in large part, are found in newly established CT measures, and to assess the complementary roles that CT and MRI can play in the functional evaluation of the lung.

RADIATION DOSE REDUCTION IN X-RAY CT

Public concern over the consequences of ionizing radiation has made it clear that, in addition to advancing methods for volumetric quantitative functional lung imaging, we must keep dose minimization as a high priority as we seek to deploy the growing armamentarium of CT-based lung imaging tools. The concerns regarding radiation dose are in part caused by increased doses delivered by MDCT scanners (22–27), their increased use and thus increased public health risk (despite low personal risk), the rapid development of a market for CT screening exams, and concerns that exams on children were being performed at adult doses (28). In addition, the 55-year Hiroshima data suggest that small but measurable risks might now be estimated. While these concerns remain controversial (24,28–30), when one considers that 2.7 million CT scans are performed on children alone, even a minor risk becomes an appreciable public health problem. There is now international pressure to target exposures at below 10 mSv when possible (31). Clearly, if the overriding goal is to provide early detection of lung diseases and quantitative tools to detect small changes in the course of a pathologic process modified by an intervention, the imaging community must address these concerns over dose. To date, low-dose CT imaging has largely been evaluated in terms of measured noise (27,32) and suitability for visual interpretation (33–39). While dose-reduction measures come primarily from the lowering of mAs with associated increased image noise, recent studies have achieved a significant dose reduction without increased noise by modulating the dose as the scanner rotates around the body (32,40–43). This allows dose reduction up to 30%–40% for typical elliptical body sections. However, the gain diminishes for circular body sections. New paradigms must be explored; and, again, care must be taken to assure that not only structural, but also functional information embedded in the reconstructed images must remain quantifiable. This means that reconstructed attenuation coefficients (Houndsfield Units [HU]) must not be corrupted by dose-reduction schemes. Newly emerging dose-reduction methods include the use of a priori knowledge from one scan to allow reduction of

dose in subsequent scans. As additional examples of how dose might be reduced, in functional studies requiring time series of axial scans (to image regional ventilation or perfusion) it is possible to lower scan dose by identifying the minimal number of time points needed to accurately assess a functional parameter, or to identify the robust curve fitting algorithms which are minimally susceptible to noise. Through improved image processing algorithms, it is expected that one can begin to significantly lower dose without effecting computer-based measures of the resultant images. Finally, through the use of complementary strengths of CT and MR, it should be possible to establish longitudinal studies which incorporate the strengths of both modalities to follow structural and functional changes in the lung.

QUANTITATIVE IMAGE ANALYSIS

Critical to taking full advantage of MDCT and MRI is the ability to objectively evaluate the information content of the images. In the case of the lung, the starting point is reliable detection of the lungs (44), lobes (45), airways (46–51), and blood vessels (52,53), followed by an analysis of parenchymal density and texture (54–56), and finally a regional quantification of ventilation (57) and perfusion (58) parameters.

EVALUATION OF THE LUNG AT ITS FUNCTIONAL INTERFACE

Computer-based methods for objective quantitation of CT data sets to compare normal and diseased lung are increasingly being used in conjunction with 2-dimensional data sets. Methods have ranged from counting the number of voxels below a cut-off (−850, −910, −950 HU) (59–70) to those which make use of measures derived from the histogram including skewness, kurtosis, etc (71). High-resolution computed tomography enhances the resolving power of the image (72–76) allowing detection of less severe emphysema. Various computer-assisted texture-based methods have successfully been used for tissue characterization. Traditional methods of texture analysis can be grouped into statistical, structural, and hybrid methods (77). Methods for tissue classification typically rely on region gray scale statistical measures (ie, mean, variance, frequency histogram) or textural measures (autocorrelation, co-occurrence matrices, run-length matrices, etc) (60,61,69,71,78–88). Lung tissue can be objectively evaluated using the density of lung tissue, either as mean lung density, or by measuring the density of lung falling below a set value (the density mask) (60,61,69,71,87). It has been shown that lung tissue mean density can be an index of emphysema (60,61,69). However, a later study showed significant lung density variation in normal individuals that could be misleading (87). A density-masking approach alone is not sufficient to distinguish normal from diseased lung (89–91). More recently, texture is increasingly being used for detection and classification of solitary pulmonary nodules.

FUNCTIONAL IMAGING

Numerous methods have been developed to assess ventilation (57), perfusion (58), or their functional outcome, gas exchange (92,93). While clearly useful, traditional pulmonary function tests are global measurements of airflow, lung volumes, and gas exchange from which are inferred primary structural and functional alterations. Imaging techniques such as positron emission tomography and the newly emerging hyperpolarized gas imaging via MRI (94–100) offer unique, complementary regional information to x-ray CT and, as they develop, are expected to offer enhancements to the knowledge base that we propose to build using x-ray CT. In the sections below we will show examples of the use of CT imaging technology to probe normal and abnormal cardiopulmonary structure and function. CT technology offers a unique and comprehensive approach to evaluating the structural and functional complexity of the respiratory and cardiopulmonary systems. It is likely that MR scanning will continue to evolve such that it will complement CT in expanding our understanding of the lung and facilitate radiation exposure reduction in human studies. The extensive tool set developed to objectively and quantitatively evaluate CT images are the gold standard that will assist in the development of MR as a complement to other imaging modalities in evaluating lung structure and function.

VENTILATION ASSESSED BY CT

The measurement of lung ventilation, lung volume, and tidal volume has traditionally been made for the entire lung, despite the fact that lung function in both health and disease is inhomogeneous. Attempts have been made

to quantify regional ventilation both directly and indirectly with a variety of invasive techniques or radioisotope imaging (101–110), but these methods have been limited by invasiveness, poor spatial and temporal resolution, qualitative nature, and/or complexity. Xenon-enhanced MDCT (Xe-MDCT) is a method for the noninvasive measurement of regional pulmonary ventilation, determined from the wash-in and wash-out rates of the radiodense, non-radioactive gas xenon as measured in serially acquired, axial CT scans. Little work had been done since the original description of this technique nearly 25 years ago (111–114), although the US Food and Drug Administration approval of Xe-MDCT for measurement of cerebral blood flow has met with moderate clinical acceptance (115). Recently, however, the application of Xe-MDCT for measurement of regional pulmonary ventilation has been updated, validated, and refined, primarily by three of the collaborators in this project, including extension of the technique to estimate regional perfusion and V/Q (57,93,116–122).

PERFUSION ASSESSED BY CT

Dynamic imaging methods have been used to estimate arterial, venous, and capillary transit times and capillary flow distributions (123–130). These methods involve two types of image data collection regimes. *Inlet–outlet detection* is typically used for conducting vessels and whole organ analysis. The other data collection regime is referred to as *residue detection*. Residue detection is typically used, alone or in conjunction with inlet detection, for analysis of microvascular regions wherein the individual vessels are below the resolution of the imaging system. Various approaches for determining blood flow and/or mean transit time have been described (124,127–137).

MRI ASSESSMENT OF LUNG FUNCTION

Over the past 10 years there has been renewed interest in applying MR imaging to the lung. Several methods have been developed that are of interest in this respect.

Proton MRI has been attempted using fast, heavily T2-weighted sequences (138) and more successfully by application of high oxygen concentration (139–141). Furthermore, combination of oxygen-enhanced ventilation imaging with techniques to visualize the lung perfusion, such as Gadolinium-enhanced and arterial spin labeling methods, has allowed further assessment of the interaction between ventilation and perfusion (96,142–144). However, several problems exist with this technology, such as the need for intravenous contrast, the inability to separate the oxygen dependent signal change in alveoli, lung tissue, and blood, and the lack of spatial and temporal resolution.

Hyperpolarized gas MRI is based on the introduction of spins into the lungs, thus allowing imaging to take place. The most commonly applied method uses hyperpolarized 3-Helium (HP 3-He), which does not cross the alveolar wall and remains entirely inert. Spin depolarization takes place as a result of the RF pulses used and the paramagnetic properties of oxygen.

HP 3-He MRI has several advantages rendering it of potential use for the purpose of functional lung imaging. First, it enables probing of the lung microstructure through diffusion imaging (apparent diffusion coefficient), which is a direct correlate for alveolar and airway size (145–148). Second, it allows the visualization of ventilation distribution at high spatial resolution (149–152). Third, it is capable of ultra-fast imaging, allowing for assessment of gas flow patterns within the lobar and segmental airways (153–155). Finally, the local rate of depolarization enables direct measurement of partial pressure of oxygen and associated gas exchange mechanism (including V/Q ratios) (156–158). In spite of these great promises, several issues of HP 3-He MRI remain to be solved, such as the intra- and inter-subject variation of signal caused by influences such as polarization level, patient characteristics, and RF coil design. This makes it even more important to compare these new methodologies with reference methods.

MODELING

Application of modern computational techniques to anatomically and biophysically based models of human physiology provides a means to integrate vast amounts of data across many spatial and temporal scales into a framework that can be linked to whole-body physiology and clinical medicine. Development of pulmonary models that can be customized to any subject means that an individual's structure can be linked to personalized predictions of function, allowing the better understanding of the influence of structural differences on imaged ventilation and perfusion, and to predict patient-specific drug deposition patterns.

COMPUTATIONAL MODELS

Integrative, anatomically based modeling takes a fundamentally different approach from traditional computational models through the incorporation of accurate descriptions of tissue properties and anatomic structure at a range of levels of interest. In this sense, the model acts as a central resource that encapsulates physiologic, anatomic, and biophysical data, but it also uses physical laws to describe the processes that determine the interaction between subsystems or substructures within the organ (eg, airways, blood vessels, parenchyma). The development of these integrative models and their associated databases has been termed the "*Physiome Project*" (159). Effort in this area over the past 10 years has primarily been focused on the heart (the Cardiome project), though work has also progressed on a Microcirculation Physiome, and an Endotheliome. Progress towards a *Lung Physiome* has been limited: having compiled a database of publications, models, and data relating to the pulmonary circulation the University of Auckland has established a web-accessible ontology for Physiome databases, including the lung, and has developed hierarchical models of pulmonary structures (160–163), which can be incorporated into a valid Lung Atlas.

COMPUTATIONAL FLUID DYNAMICS

As a first step in understanding image-based measures in terms of structure-function relationships, the role played by the properties of contrast agents (iodinated compounds used for assessing blood flow (92) or dense gases such as xenon and krypton (57,164), or lighter gas such as helium to assess regional ventilation (16,21,165–167) must be understood. Computational fluid dynamics techniques are used currently to predict particle deposition patterns in the lung but have been limited to artificial geometries and a few generations of airways. Furthermore, little attention is paid to gas flow, particularly as it relates to significant departures from standard room air mixtures of O_2, CO_2, and N_2. Accurate representation of the geometry of organs is critically important when modeling physiologic behavior, although the structural components or level of detail required in a model is particular to the functional problem to which it is applied. The method for generating computational meshes from imaging data and the degree of anatomic accuracy and complexity will depend on the task at hand (168,169).

Simulation of ventilation distribution requires computational meshes that extend through the entire conducting airway system. However, image-derived data can be used to create meshes of only a portion of the tree. A further technique is required to extend this image-derived tree out to the terminal conducting airways. This can be accomplished by attaching airway segments that have dimensions based on either the Weibel symmetric (170) or Horsfield asymmetric (171) models, but neither of these idealized models includes spatial positioning or relate to the geometry of an individual. The Kitaoka algorithm (172) can be used to grow an airway-like structure into idealized lobe shapes; however, it does not yet allow generation into anatomically realistic (imaging-based) volumes. Tawhai et al (161) have developed an algorithm to generate host-volume dependent airway-consistent models. The ability to fill any shaped host volume means that the airway models can be customized to individual geometry, allowing us to predict ventilation distribution for an individual.

Simulation of blood flow is approached differently for the large pulmonary vessels and the microcirculation and there is a need to provide the linkage between these two vascular bed components if we are to understand the perfusion side of functional heterogeneity in health and disease. Linking large vessel perfusion predictions in customized vessel models to anatomically based microvasculature models such as Burrowes et al (162) will provide a tool for investigating inter-individual differences in cell transit times that may contribute to differences in the pattern of development of, for example, emphysema. In the larger vessels the blood is treated as a Newtonian fluid and its transport can be simulated by solution of Navier Stokes equations, which can be reduced to 1 dimension. One-dimensional models of vascular blood flow have been developed to model flow through relatively simple network geometries (173–175), and to model transient flow through an anatomically based coronary artery model (176). Reduction of the governing equations to 1 dimension is attractive computationally; however, we expect that this reduction may not be suitable for all simulation conditions (eg, high flow), or all physical locations (eg, largest vessels). Blood transported through the microcirculatory vessels is non-Newtonian and requires governing equations that incorporate its two-phase nature, and changes in hematocrit and vessel resistance (177). The classic sheet-flow model (178) for the pulmonary microcirculation has contributed much to our under-

standing of the system, but to investigate the distribution of transit times of blood cells requires a model that includes the segmented structure of the capillary bed (162).

LUNG ATLAS

A consortium of investigators (including the authors of this special review) have embarked on a project over the past 5 years to establish a normative atlas of the human lung for four decades of age range for both the male and female lung (1). These evolving electronic atlases of the lung (atlases specific to age and gender) serve to house our knowledgebase of the lung. Developing standardized lung atlases is important for defining normal ranges of anatomic shape and function, standardizing nomenclature, illustrating anatomy and function, and defining a standard coordinate system for reporting anatomic and functional observations. When complete, the lung atlases will contain information such as textual annotations (XML, FieldML, etc), physiome ontology (see below), hyperlinks, segmentations, surfaces, surface curvature, material properties, FEM descriptions, and CT/MR image data non-rigidly registered to the atlas coordinate system. The atlas coordinate system will provide a standard for reporting anatomic and functional observations across patients and research labs, ie, it will allow statements such as perfusion was reduced by 20% at atlas coordinate "350, 457, 168" in the emphysema population compared with the normal population.

DEFORMABLE MODELS

An electronic deformable image atlas can change its shape to adjust to individual differences. This is accomplished by a mapping or transformation that relates corresponding points in the coordinate system of the atlas with the implicit coordinate system of a target medical image from an individual. The transformation maps the information from the atlas to the individual producing an individualized atlas, ie, a new knowledgebase describing the individual. Abnormalities in anatomic shape and function can be located and quantified based on the parameters in the individualized atlas that exceed normative values defined by the original atlas.

As defined above, the atlas itself is a model. Because an atlas fully describes an object, it can include a variety of models, provided that they are referenced to the coordinate system of the atlas. Hence, computational geometric models such as FEM models, point distribution models, and probabilistic shape distributions on images can all be part of the atlas (once the images are associated with the coordinate system of the atlas) and can be used to model shape, motion, disease, or any other desired information. Information derived or gleaned from the various computation models contained within the atlas becomes part of the knowledge base associated with the lung. A large body of literature has been published on medical image registration techniques (179–181). Registration methods in the medical image domain focus primarily on the brain (182–199), but also other organ systems, such as the spine (200), inner ear (201), breast (202), and cervix (203). To date, few groups (9,10,204–209) have concentrated on lung image registration, and very little work has been performed to incorporate the airway, vasculature, and lobar structure of the lung in the image registration algorithms.

CONCLUSION

With the growing understanding of the environmental and genetic basis of lung disease, the rapid evolution of potentially beneficial interventions to lung disease, and the use of the inhaled route for systemic drug delivery, there is a need for multidisciplinary efforts to advance the field of lung imaging. While there have been dramatic advances in imaging methodologies including multidetector row CT, hyperpolarized gas MRI, positron emission tomography, SPECT, new endobronchial imaging methods, and more, these advances bring a growing challenge to the community to develop standards for imaging protocols, objective and quantitative methods for image analysis, tools for establishing normative databases, and more. As the need grows for "team science," so too grows the need for forums where scientists of varying backgrounds can simultaneously find a place to exchange ideas. In the field of lung imaging, we would like to thank *Academic Radiology* for stepping up to the plate.

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