10-15-2019

Visualization of the Small Airways:What It Is and Why It Matters

Mark L Schiebler

Grace Parraga

Radiology

Visualization of the Small Airways: What It Is and Why It Matters

Mark L. Schiebler, MD • Grace Parraga, PhD

Dr Mark L. Schiebler is a professor of cardiothoracic imaging in the Department of Radiology at the University of Wisconsin-Madison. His research interests are in the diseases of the small airways and coronary arteries and how imaging biomarkers and computational fluid dynamics can be used for more cost-effective patient outcomes. Dr Schiebler is the current chairman of the board of the International Workshop for Pulmonary Functional Imaging. He also serves as the deputy editor of Thoracic Imaging for *Radiology*

Dr Grace Parraga is a professor in the Department of Medical Biophysics and Imaging Research Laboratories at Robarts Research Institute, both at Western University, London, Canada. Her laboratory focuses on developing CT and MRI tools to provide a deeper understanding of chronic lung disease initiation, progression, and response to therapy. Her lab is home to 20 trainees and staff, and she has trained over 150 students and fellows in the past 15 years.

When the earth transitioned to an oxygen-containing atmosphere, many bacterial species were killed by the free radicals that developed in their cytoplasm. New life forms took advantage of this change by evolving to use oxygen as the final resting place for electrons involved in the Krebs cycle. Animals today rely on getting oxygen into the blood stream and getting carbon dioxide out by ventilation through sequentially smaller and smaller tubes until diffusion takes over, finally reaching the terminal respiratory bronchiole and its associated alveoli for gas exchange. All animals are obligate aerobes. One group (1) has estimated that there are 274 to 790 million alveoli in the healthy adult lung. In this issue of *Radiology*, Kim et al (2) describe a visualization method to study the invisible small airways (seven to 30th generation) that move air from the trachea to the peripheral airways and back again for normal ventilation.

Enumerating the health, composition, number, and location of the small airways is an important goal for chest imaging and research. Whereas current thin-section chest CT routinely shows sixth-order branching of the tracheobronchial tree, unless the airway is diseased or plugged, smaller airways from the seventh to 30th generation are not seen because they are below the resolution of current clinical CT hardware. In this issue, Kim et al (2) describe a method, named full-scale airway network (FAN), to begin to model and study these important structures. The method is derived from computational fluid dynamics (modeling airflow instead of fluid) to achieve an idealized representation of the likely number of branching elements, their location, and the effective lumen size of all the bronchial structures to the level of the alveolus. Lin and colleagues (3) used a similar approach to show particle depositions within the lung for determining the optimal sizes for drug therapy aerosols. By using the FAN modeling approach, we now have a tool to probe the role of disease on the lung microstructure in health and disease. We feel that the FAN model is an important advance in respiratory research.

Diseases of the lung are important for world health. Chronic obstructive pulmonary disease (COPD) will be the third most important cause of mortality in the world by 2020 (4). The inability to breathe is life threatening, and difficulty breathing (with or without supplemental oxygen) adds significant morbidity to the activities of daily life. How should we study the changes in the lung that occur with smoking and air pollution? The role of inhaled microparticulates from air pollution and cooking indoors by using biofuels has been shown to adversely affect lung function (5).

It is reasonable to ask what research questions are now answerable with the FAN method. Whereas there are many possible answers to this question, it is most likely that the area that will show the most activity revolves around the issue of how particulates affect small airway disease. How air pollution and occupational lung diseases impact the lumen of the seventh to 30th generation bronchi is going to be the major advance of this method. With the many microparticulates from air pollution becoming a larger issue in metropolitan areas, this tool has the opportunity to help us determine its importance on lung function at a personalized level. For the workers who have occupational exposure to silica and coal dusts this tool may also be useful in showing the individualized burden of disease. The use of fractals,

From the Department of Radiology, Professor of Cardiothoracic Radiology, University of Wisconsin School of Medicine and Public Health, 600 Highland Ave, Madison, WI 53792-3252 (M.L.S.); and Department of Medical Biophysics and Robarts Research Institute, Western University, London, Canada (G.P.). Received September 6, 2019; revision requested September 17; revision received September 19; accepted September 20. **Address correspondence to** M.L.S. (e-mail: *mschiebler@uwhealth.org*).

M.L.S. supported by National Heart Lung and Blood Institute (RFA-HL-11-018). G.P. supported by Canadian Institutes of Health Research (CIHR) and Natural Sciences and Engineering Council (NSERC) Canada funding.

Conflicts of interest are listed at the end of this article

See also the article by Kim et al in this issue.

Radiology 2019; 293:674–675 • https://doi.org/10.1148/radiol.2019192025 • Content code: CH

a mathematical method for determining the branching pattern of structures, directly enumerates the simplification of airways in COPD (6). It will be of interest to discover how the FAN method helps to elucidate the number of airways in healthy adults and their fractal dimension. It is likely that these values will change in health, disease, and with aging. It is easy to imagine that pediatric and adult nomograms for airway numbers and fractal dimension will become another metric by which to measure lung maturation and health (7). Enumeration of the change in number of airways to document therapeutic response or disease progression could also become important.

Recently, micro-CT has been used for the ex vivo evaluation of inflated frozen human lung specimens. This approach allows for the visualization of the three-dimensional structure of the lung down to the level of the terminal bronchioles. The lack of fixative also enables subsequent comparison with the cellular matrix and gene expression changes that occur with disease. By using such micro-CT methods, Tang et al (7) also showed in animal studies that air pollution adversely affects fetal lung growth.

The use of fractals, a mathematical method for determining the branching pattern of structures, directly enumerates the simplification of airways in COPD and pulmonary arteries in pulmonary hypertension (6,8). It will be of interest to discover how the FAN method helps to further elucidate the number of airways in healthy adults and their fractal dimension. It is likely that these values will change in health, disease, and with aging. It is easy to imagine that pediatric and adult nomograms for airway numbers and fractal dimension will become another metric by which to measure lung maturation and health. Enumeration of the change in number of airways to document therapeutic response or disease progression could also become important.

The limitations of the modeling method presented by Kim et al (2) are still unknown because their method was only demonstrated in nine patients with COPD. However, at a minimum there needs to be validation of this approach with ex vivo histologic examination and/or micro-CT imaging in healthy and diseased lungs. The model relies on the expected flow of gas to a terminal location (the alveoli) but this does not account for remodeling of the airway from disease, and so the mathematics can only show an average lumen size, average length of a bronchiole, average angle of a bifurcation, and the likely location within the lung. There remain other questions as well: Does the model account for tapering from the beginning of a segment to the branch point? Does the model identify collapsibility of the airway at expiration? What is the influence of the use of −950 HU as the cutoff for emphysema when the examination was not performed at full inspiration (total lung capacity)? And, finally, will the computation of the model change when tissue density is calculated at 37°C instead of 0°C? The good news here is that all of these reservations regarding the quality of the model are testable and the FAN model can be modified to more closely approximate the truth.

With the introduction of computational methods and advanced programming, imaging science is leading medicine to ways of understanding the body's response to disease. The sharing of methods so that others can reproduce published results is, however, potentially problematic if the code is not published. For the authors, publishing the code means that it can no longer be patent protected, limiting its potential future commercial value. Thus, there is a tug-of-war between publishing one's study with access to the code that can be used by others to replicate the results and the desire to have a commercial product. Importantly, the modeling software developed by Kim et al (2) will be made available to other potential users so they can build on their results.

The ability to study a relatively unknown region of the body is exciting. This is unexplored territory for scientific researchers and should promise to be of more than just academic interest. For example, if we can learn how to limit or prevent lung destruction from air pollution, cannabis, and tobacco smoke and/or vaping, this could serve to substantially improve the lives of many who are exposed to these materials. For those with asthma, learning how to modify the response of the small airways to antigens will be key in helping their pulmonary function. We know that lung function decreases as we age (9). Perhaps the FAN method will show that remodeling and simplification of the bronchial structures helps to explain this fact. Knowing what happens to the airways will allow investigators to research methods that can act to keep the lungs youthful. We look forward to future innovations on the basis of modeling of the small airways.

Disclosures of Conflicts of Interest: M.L.S. Activities related to the present article: disclosed no relevant relationships. Activities not related to the present article: disclosed money paid to author for patents; disclosed stock/stock options in Healymyen, Stemina Biomarker Discovery, and X-Vax. Other relationships: disclosed no relevant relationships. **G.P.** disclosed no relevant relationships.

References

1. Ochs M, Nyengaard JR, Jung A, et al. The number of alveoli in the human lung. Am J Respir Crit Care Med 2004;169(1):120–124.
2. Kim M, Doganay O, Matin TN, Povey T, Gleeson FV. CT-based airway flow model to assess ventilation in chronic obstructive pulmonary disease: a pilot study. Radiology 2019;293:666–673.
3. Lin CL, Tawhai MH, Hoffman EA. Multiscale image-based modeling and simulation of gas flow and particle transport in the human lungs. Wiley Interdiscip Rev Syst Biol Med 2013;5(5):643–655.
4. Vestbo J, Hurd SS, Agustí AG, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med 2013;187(4):347–365.
5. Grobbelaar JP, Bateman ED. Hut lung: a domestically acquired pneumoconiosis of mixed aetiology in rural women. Thorax 1991;46(5):334–340.
6. Bodduluri S, Puliyakote ASK, Gerard SE, et al. Airway fractal dimension predicts respiratory morbidity and mortality in COPD. J Clin Invest 2018;128(12):5374–5382.
7. Tang W, Huang S, Du L, et al. Expression of HMGB1 in maternal exposure to fine particulate air pollution induces lung injury in rat offspring assessed with micro-CT. Chem Biol Interact 2018;280:64–69.
8. Helmberger M, Pienn M, Urschler M, et al. Quantification of tortuosity and fractal dimension of the lung vessels in pulmonary hypertension patients. PLoS One 2014;9(1):e87515.
9. Lowery EM, Brubaker AL, Kuhlmann E, Kovacs EJ. The aging lung. Clin Interv Aging 2013;8:1489–1496.