Imaging in Aerosol Medicine

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Imaging techniques have been used extensively to study the delivery of inhaled medications. Deposition scintigraphy involves the quantification of deposited aerosol dose and is performed using 2-dimensional planar or 3-dimensional positron emission tomography (PET) or single-photon-emission computed tomography (SPECT) imaging techniques. Planar techniques have an extensive history of use, and quantification methods are well established. SPECT and PET techniques can provide better dose localization, but quantification is more complex, and the techniques are in more limited use. Aerosols have also been used to deliver radiopharmaceutical probes for the imaging of lung physiology. These studies include measurements of ventilation, mucus and cough clearance, and, more recently, liquid absorption in the airways. Clearance measurements have been used to assess therapeutic response in conditions such as cystic fibrosis. Future directions in aerosol-based imaging are likely to include use of novel probes to measure new physiological processes in the lung, more thorough integration of anatomical imaging, and use of multiple probes to simultaneously image drug and disease or interacting physiological processes. *Key words: aerosol deposition; aerosol scintigraphy; mucus clearance; lung imaging; molecular imaging; nuclear imaging.* [Respir Care 2015;60(6):850–857. © 2015 Daedalus Enterprises]

Introduction

A key aspect in the development of inhaled medications is the measurement and optimization of deposited aerosol dose. The use of imaging techniques to measure aerosol drug deposition has followed the development of more complex inhaled therapies and the invention of more advanced aerosol delivery technologies. Deposition scintigraphy techniques provide quantitative information on aerosol deposition using the radioactivity associated with an added radiopharmaceutical as an analog for drug dose. Nuclear imaging cameras can depict the deposited aerosol within the body, allowing for regional dose quantification. Deposition scintigraphy techniques have evolved along with nuclear imaging technology, and a variety of 2-dimensional and 3-dimensional techniques are now in use, some of which include anatomical imaging. These techniques have been applied with medical nebulizers, metered-dose inhalers, and powder inhalers and used in par-

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allel with pharmacokinetic measurements. Aerosols have also been used to deliver radiopharmaceutical probes to the lungs for physiological imaging purposes. These aerosol-based imaging techniques allow measurements of ventilation, permeability, liquid absorption, and clearance in the lungs. In some cases, these measurements have proved to be a valuable outcome measure for therapeutic development.

Techniques to Assess Aerosol Delivery

The importance of quantifying deposited aerosol dose can be appreciated by considering medications with narrow therapeutic indices, such as insulin, or with no immediate indication of clinical effect, such as an inhaled steroid. Dosing variability in aerosol drug delivery is well documented, especially in the setting of lung disease. Deposition scintigraphy can be used to quantify and optimize delivered aerosol dose and dosing variability ahead of the performance of pivotal clinical studies.

Deposition scintigraphy involves the use of either direct or indirect radiopharmaceutical labels. Technetium-99m (^{99m}Tc) is often used for this labeling based on its strong imaging signal and its limited half-life (6 h).[1] Indirect labeling is performed by adding an approved ^{99m}Tc compound, such as ^{99m}Tc-diethylenetriamine penta-acetic or ^{99m}Tc-sulfur colloid, to an aerosol medication and demonstrating that the radioactivity associated with the ^{99m}Tc distributes proportionally to the active drug content throughout a range of different aerosol sizes.[2] Direct labeling can often be performed through stannous reduction of ^{99m}Tc before addition to the active drug.[3] If performed successfully, the ^{99m}Tc is then bound directly to the active drug. Techniques for establishing and validating these labels are described in the literature.[4]

Once a labeling method is established, a combination of the inhaled medication and the radiopharmaceutical is delivered using a clinically applicable delivery system. The radioactivity associated with ^{99m}Tc acts as an analog for drug dose. It can be measured in the delivery system before and after delivery to determine the total delivered dose (a mass balance technique). When specific calibrations are in place, total deposited dose can also be determined directly from gamma camera images. Figure 1 includes a planar image of a lung transplant recipient performing a deposition scintigraphy study. These images provide both a qualitative picture of aerosol deposition in the lungs and a means to quantify the dose in different deposition zones. Quantification of deposited dose from gamma camera images involves a series of corrections typically including decay, background, and attenuation correction and the use of geometric mean averages of anterior and posterior images to account for the different distances between the organs and the camera. Regional dosing may be determined by simply dividing up the total planar image counts by region. Reviews of these techniques have been published as part of attempts to standardize them for multi-center use.[5]

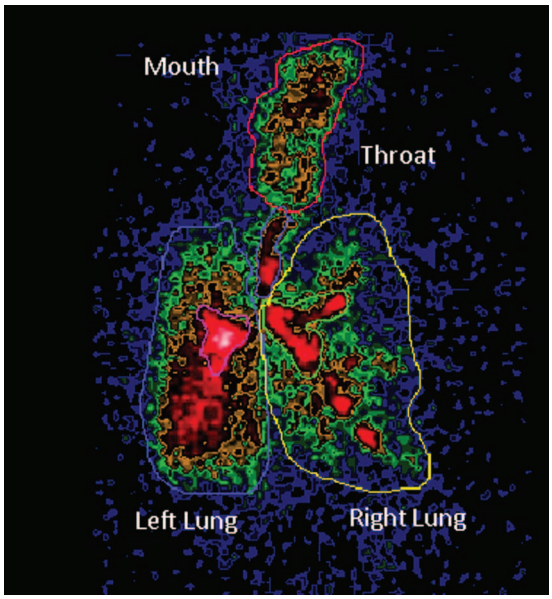

Fig. 1. Planar image depicting aerosol deposition in a lung transplant recipient.

Typically ~148 MBq (4 mCi) of ^{99m}Tc is added to a nebulizer for a deposition scintigraphy scan. The associated radiation exposure after inhalation depends on the efficiency of the delivery system, the physiological and radiological half-life of the radiopharmaceutical in use, and the size (age) of the patient. As an example, a 148-MBq dose of ^{99m}Tc-sulfur colloid delivered with 20% efficiency would result in an internal dose of 29.6 MBq (0.8 mCi), which would be associated with an estimated effective dose equivalent exposure of 0.44 mSv (44 mrem) for an adult subject.[6] This is ~14% of yearly natural background exposure.[7] These exposure levels are low enough to allow multiple studies and pediatric applications.

Nebulizer delivery systems are the simplest to assess using deposition scintigraphy methods because the active drug is directly accessible for labeling. Many examples of deposition studies with nebulizers are available in the literature.[2,8-12] These studies were instrumental in demonstrating the significant intersubject variability associated with nebulized drug delivery and contributed to the development of new and more precise delivery systems. Studies with metered-dose inhalers require on-site canister charging after drug labeling and thus pose more complications.[13-17] The labeling of powders presents even more substantial complications because the labeling technique must be applied without affecting the shape or size of the drug particles. This can be accomplished by incorporating

the radiolabel ahead of the powder formation process[18,19] or through careful processing of the existing powder.[20,21]

Gamma cameras have one or more imaging heads that contain a series of individual crystal or solid-state gamma-ray detectors. A single gamma camera head can capture a planar image similar to that shown in Figure 1. Two gamma camera heads positioned 180° from each other can provide simultaneous anterior and posterior planar images. Stepwise rotation of the gamma camera heads can be used to generate a series of planar images at different locations around the body that can then be processed to generate a 3-dimensional depiction of the radiopharmaceutical in the body. This process also generates a series of transverse, coronal, and sagittal views. This is the basis of single-photon-emission computed tomography (SPECT) imaging. SPECT studies use radioisotopes similar to those described for planar scintigraphy. SPECT scans of aerosol deposition can provide exact localization of deposited dose within the 3-dimensional anatomy of the lung. In planar images, many lung structures are overlaid, making it impossible to completely differentiate between airway and alveolar deposition. SPECT imaging allows better differentiation of these structures and may allow for the isolation of specific anatomical regions. In many cases, SPECT cameras offer the option of collecting and co-registering a computed tomography (CT) or magnetic resonance imaging (MRI) scan. This can be placed onto the SPECT image to depict aerosol deposition and lung anatomy together, thus allowing for even more specific localization of aerosol deposition. However, quantification of aerosol deposition in SPECT imaging requires more complex techniques compared with those for planar imaging and longer imaging periods, and these techniques are generally used less often.[22-24]

Positron emission tomography (PET) uses different radioisotopes, which emit a positively charged electron (position). Positrons travel a short distance in the body before interacting with an electron, causing annihilation and emission of 2 high-energy gamma rays in exactly opposite directions. Having 2 signals at a fixed orientation provides better signal localization and ultimately better resolution than SPECT. CT or MRI is often included with PET in the same scanner. PET has been used for aerosol imaging by a limited number of centers.[25,26] PET radiopharmaceuticals generally have shorter half-lives. The most commonly used PET radioisotope, fluorine-18, has a half-life of 110 min. A wide variety of PET radiopharmaceuticals have been produced, some including PET emitting carbon-11, which could potentially be synthesized into many active drugs.[27]

MRI-based techniques have been considered for use in assessing deposited aerosol dose. These techniques offer the advantage of measurement without ionizing radiation exposure. One historic drawback of MRI in lung imaging is the imaging artifacts associated with lung expansions and contractions during the extended MRI scan time. Newer scanning techniques have largely removed these obstacles.[28] However, aerosols in these techniques need to include a contrast agent, such as gadolinium, to be detectable. Gadolinium-based deposition measurement techniques have been demonstrated in animal studies, but the required contrast amounts limit the potential for human use at this time.[29] Hyperpolarized gases are being utilized to illustrate ventilation through MRI. If a human-suitable contrast agent for aerosols could be found, this modality might allow for simultaneous imaging of ventilation and aerosol deposition.

Imaging techniques for measuring deposited doses of aerosol drugs in the lung will continue to play a role in the development of new inhaled medications and delivery devices. This includes a role in initial dose selection and in estimating population dosing variability. More sophisticated applications might include the use of multiple, tightly controlled dosing levels to determine dose-to-effect relationships. Deposition studies have, in some cases, been integrated into pharmacokinetic testing, which is a staple of medication development.[2] This combination of techniques provides a full picture of the kinetics of inhaled drug delivery. Recent attempts have been made to standardize the techniques used to perform deposition scintigraphy studies, providing a basis for application through multi-center studies.[4,5,24,25,30] This standardization may also facilitate a regulatory role for these techniques. Simple validation of sufficient dosing at sites of proposed action would seem to justify this regulatory role. Table 1 includes a summary comparison of available imaging modalities.

Aerosol-Based Physiology Measurements

Aerosolized radiopharmaceuticals are used in a variety of clinical and experimental functional nuclear imaging procedures. In these studies, radiopharmaceutical probes are used to measure specific aspects of lung physiology. Aerosol-based ventilation scans are commonly performed in nuclear medicine departments. These scans utilize nebulized ^{99m}Tc-diethylenetriamine penta-acetic aerosols to measure lung ventilation. An injected radiopharmaceutical particle probe is then typically utilized to measure perfusion (ventilation/perfusion scan). These scans can be used to detect pulmonary emboli or ventilation/perfusion mismatching in the lungs.

Aerosol-based imaging has a long history in experimental studies of lung physiology. One common experimental application is the measurement of lung clearance. A non-absorbable radiolabeled probe is typically delivered into the lungs. It becomes suspended in the mucus in the airways. Serial gamma camera images are collected over extended periods to measure the clearance of the mucus through mucus or cough clearance. These host-defense

Table 1. Comparison of Various Imaging Modalities for Aerosol-Based Techniques (Deposition or Physiology)

Technique	Advantages	Disadvantages	Citation
Planar scintigraphy	Established quantification techniques, available standardized procedures	Poor representation of 3-dimensional lung anatomy	Newman et al[5]
3-Dimensional SPECT scintigraphy	3-Dimensional imaging, potential to localize sites of disease through co-registration with CT/MRI	Long imaging times possibly not suitable for physiology, more complex quantification	Fleming et al[24]
3-Dimensional PET scintigraphy	3-Dimensional imaging, potential to localize sites of disease through co-registration with CT/MRI, potential for directly labeled drugs or sophisticated physiology probes	More complex radiopharmaceutical production, often short-lived radiopharmaceuticals	Dolovich and Bailey[25]
MRI	3-Dimensional imaging, potential to localize sites of disease, potential for simultaneous imaging of ventilation	Human use limited by required large amounts of current contrast agents	Thompson and Finlay[29]

SPECT = single-photon-emission computed tomography
CT = computed tomography
MRI = magnetic resonance imaging
PET = positron emission tomography

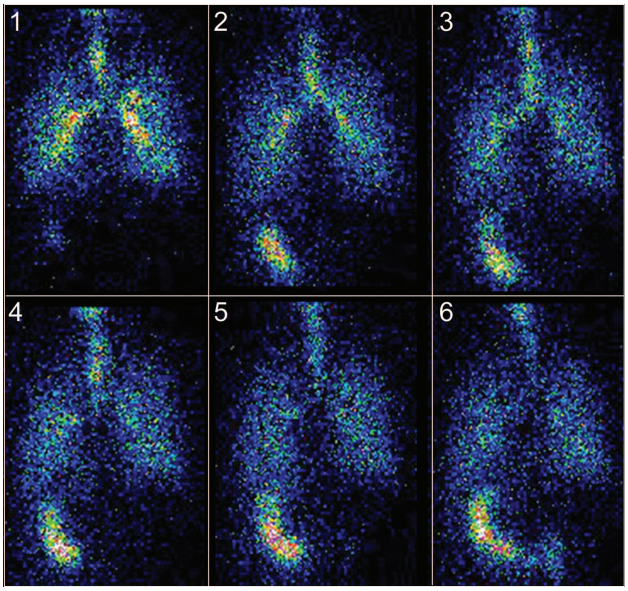

Fig. 2. Mucociliary clearance of radiolabeled particulate from the large airways depicted over ~60 min.

mechanisms are vital to protecting the lungs from inhaled pathogens and particulate. Their failure in diseases such as cystic fibrosis can lead to life-threatening opportunistic infections. Mucus clearance scans have been applied to test new medications for cystic fibrosis. In some cases, these imaging methods may provide indications of therapeutic efficacy ahead of other outcome measures.[31-33] Figure 2 shows example images depicting mucus clearance.

Radiolabeled small-molecule probes have been delivered to the lungs by aerosol to assess lung permeability. These probes can be absorbed into the bloodstream, and their rate of clearance has been used as an indication of lung inflammation and injury. Increases in the absorption rate of radiolabeled diethylenetriamine penta-acetic have been demonstrated in smokers[34] and in subjects with inflammatory diseases such as asthma.[35] Small-molecule probes have also been developed to detect changes in airway liquid absorption. In these studies, a multiprobe method is utilized. A particle probe is delivered along with a small-molecule probe in the same aerosol. This small molecule is removed from the lungs through both absorption and mucus clearance, whereas the particle is removed only by mucus clearance. Each probe has a different radiolabel, so they can be independently tracked. The difference in the clearance rates of the probes provides an estimate of the absorption rate of the small-molecule probe. These absorptive clearance rates have been shown to be related to liquid absorption by in vitro studies and increased in the airways of patients with cystic fibrosis. Airway liquid hyperabsorption is a key aspect of cystic fibrosis lung pathophysiology that would be expected to change rapidly with a successful therapy, and this technique is being developed to rapidly screen new cystic fibrosis medications.[36,37]

Limitations of Aerosol-Based Techniques

Much of the experience in measuring aerosol deposition using imaging techniques was obtained through studies of uniform solutions delivered with jet nebulizers. As inhaled drug development moves more toward the use of powders, suspensions, and complex large molecules, new labeling and validation techniques will be required. Techniques that could be applied more generally across different preparations with similar characteristics would be particularly useful.

Aerosol-based physiology techniques are ultimately limited by the methods used to deliver aerosol probes. More

targeted delivery techniques would allow for more specific assessments, for example, better isolation of small airways from alveoli. In this regard, novel aerosol technologies designed to target drug delivery may find a second application in the assessment of lung physiology. All of these techniques are limited by the spatial resolution provided by the imaging modality. No current modality is capable of imaging the smallest airways or alveoli. Physiological imaging methods are further limited by the temporal resolution of the imaging modality.

Future Developments

PET imaging provides unique opportunities for physiological lung imaging. The increased resolution of these techniques can provide local assessments that may not be possible with other modalities. A wide variety of PET probes can be produced by cyclotron. These include molecules such as carbon-11, nitrogen-13, fluorine-18, and oxygen-15. These basic molecules can be used to generate simple probes, such as ^{13}N-labeled ammonia or ^{15}O-labeled water, or more complex probes, such as active drug molecules or antibodies. Many specific PET probes have been developed to quantify aspects of physiology such as cell metabolism, tumor growth, angiogenesis, and formation of the extracellular matrix.[38-41] PET probes are commonly used to detect the increased metabolic rate associated with tumor growth. Other injected PET probes have already been used in studies of ventilation, perfusion, and inflammation.[42] However, very little work has been done with aerosol delivery. The attraction of this route is direct access to the pulmonary epithelium. As described above, PET methods provide improved resolution and can be overlaid on matching CT or MRI scans collected in the same scanner, thus allowing for exact localization. Drawbacks to PET methods include the very limited half-life of some of the positron emitters and the extensive facilities required to produce them.

Most new nuclear imaging scanners combine a functional imaging modality (SPECT or PET) with an anatomical imaging method (CT or MRI). This mixed-modality imaging allows drug doses or physiological measurements to be more exactly located. This is particularly advantageous given the complex 3-dimensional structure of the lung. Lung MRI, which was generally not considered useful in the past because of the motion artifacts associated with breathing, is becoming more common.[28,43] This modality could potentially provide finer resolution than has previously been available through CT scans and spare patients the significant radiation burden associated with CT.

We had previously described the aerosol delivery of multiple radiolabeled probes to the lungs to measure absorptive clearance (liquid absorption) in the airways.[37] In those studies, the combination of the probes provided information that was not available with a single probe. These probes were independently resolvable because they were tagged with different radioisotopes, specifically indium-111 and ^{99m}Tc. New imaging techniques could be designed based on a differential method such as this or a co-localization method. An intriguing example would be an imaging technique that independently depicts pathophysiology and therapeutic delivery in the lung. Consider, for example, an aerosol deposition study of an inhaled steroid that also includes a depiction of lung inflammation or a chemotherapeutic that could be localized to the site of a tumor. Delivery techniques could be tuned as part of the development process or customized to specific patients. As imaging technologies and probe developments advance, such measurements may become feasible and provide new insights into disease treatments. More precise aerosol drug delivery technologies would allow for easier and more precise application of these techniques to the lungs.

REFERENCES

1. Kuni C, duCret, RP. Manual of nuclear medicine imaging. New York: Thieme Medical Publishers; 1997.
2. Corcoran TE, Niven R, Verret W, Dilly S, Johnson BA. Lung deposition and pharmacokinetics of nebulized cyclosporine in lung transplant patients. J Aerosol Med Pulm Drug Deliv 2014;27(3):178-184.
3. Saha G. Fundamentals of nuclear pharmacy, 5th edition. New York: Springer; 2004.
4. Devadason SG, Chan HK, Haeussermann S, Kietzig C, Kuehl PJ, Newman S, et al. Validation of radiolabeling of drug formulations for aerosol deposition assessment of orally inhaled products. J Aerosol Med Pulm Drug Deliv 2012;25(Suppl 1):S6-S9.
5. Newman S, Bennett WD, Biddiscombe M, Devadason SG, Dolovich MB, Fleming J, et al. Standardization of techniques for using planar (2D) imaging for aerosol deposition assessment of orally inhaled products. J Aerosol Med Pulm Drug Deliv 2012;25(Suppl 1):S10-S28.
6. International Commission on Radiological Protection. Radiation dose to patients from radiopharmaceuticals. Ann ICRP 1988;18(1-4):ICRP publication 53.
7. United States Nuclear Regulatory Commission. Fact sheet on biological effects of radiation. http://www.nrc.gov/reading-rm/doc-collections/fact-sheets/bio-effects-radiation.html. Accessed *September 26, 2014*.
8. Amirav I, Balanov I, Gorenberg M, Luder AS, Newhouse MT, Groshar D. Beta-agonist aerosol distribution in respiratory syncytial virus bronchiolitis in infants. J Nucl Med 2002;43(4):487-491.
9. Nikander K, Prince I, Coughlin S, Warren S, Taylor G. Mode of breathing–tidal or slow and deep–through the I-neb adaptive aerosol delivery (AAD) system affects lung deposition of ^{99m}Tc-DTPA. J Aerosol Med Pulm Drug Deliv 2010;23(Suppl 1):S37-S43.
10. O'Riordan TG, Palmer LB, Smaldone GC. Aerosol deposition in mechanically ventilated patients. Optimizing nebulizer delivery. Am J Respir Crit Care Med 1994;149(1):214-219.
11. Behr J, Zimmermann G, Baumgartner R, Leuchte H, Neurohr C, Brand P, et al. Lung deposition of a liposomal cyclosporine A inhalation solution in patients after lung transplantation. J Aerosol Med Pulm Drug Deliv 2009;22(2):121-130.

12. Ilowite JS, Gorvoy JD, Smaldone GC. Quantitative deposition of aerosolized gentamicin in cystic fibrosis. Am Rev Respir Dis 1987; 136(6):1445-1449.
13. Newman SP, Pitcairn GR, Adkin DA, Vidgren MT, Silvasti M. Comparison of beclomethasone dipropionate delivery by Easyhaler dry powder inhaler and pMDI plus large volume spacer. J Aerosol Med 2001;14(2):217-225.
14. Devadason SG, Huang T, Walker S, Troedson R, Le Souëf PN. Distribution of technetium-99m-labelled QVAR delivered using an Autohaler device in children. Eur Respir J 2003;21(6):1007-1011.
15. Pitcairn G, Reader S, Pavia D, Newman S. Deposition of corticosteroid aerosol in the human lung by Respimat Soft Mist inhaler compared to deposition by metered dose inhaler or by Turbuhaler dry powder inhaler. J Aerosol Med 2005;18(3):264-272.
16. Leach CL, Bethke TD, Boudreau RJ, Hasselquist BE, Drollmann A, Davidson P, Wurst W. Two-dimensional and three-dimensional imaging show ciclesonide has high lung deposition and peripheral distribution: a nonrandomized study in healthy volunteers. J Aerosol Med 2006;19(2):117-126.
17. Brand P, Hederer B, Austen G, Dewberry H, Meyer T. Higher lung deposition with Respimat Soft Mist inhaler than HFA-MDI in COPD patients with poor technique. Int J Chron Obstruct Pulmon Dis 2008; 3(4):763-770.
18. Glover W, Chan HK, Eberl S, Daviskas E, Verschuer J. Effect of particle size of dry powder mannitol on the lung deposition in healthy volunteers. Int J Pharm 2008;349(1-2):314-322.
19. Newman S, Malik S, Hirst R, Pitcairn G, Heide A, Pabst J, et al. Lung deposition of salbutamol in healthy human subjects from the MAGhaler dry powder inhaler. Respir Med 2002;96(12):1026-1032.
20. Ball DJ, Hirst PH, Newman SP, Sonet B, Streel B, Vanderbist F. Deposition and pharmacokinetics of budesonide from the Miat Monodose inhaler, a simple dry powder device. Int J Pharm 2002;245(1-2):123-132.
21. Hirst PH, Bacon RE, Pitcairn GR, Silvasti M, Newman SP. A comparison of the lung deposition of budesonide from Easyhaler, Turbuhaler and pMDI plus spacer in asthmatic patients. Respir Med 2001;95(9):720-727.
22. Majoral C, Fleming J, Conway J, Katz I, Tossici-Bolt L, Pichelin M, et al. Controlled, parametric, individualized, 2D and 3D imaging measurements of aerosol deposition in the respiratory tract of healthy human volunteers: in vivo data analysis. J Aerosol Med Pulm Drug Deliv 2014;27(5):349-362.
23. Conway J, Fleming J, Bennett M, Havelock T. The co-imaging of gamma camera measurements of aerosol deposition and respiratory anatomy. J Aerosol Med Pulm Drug Deliv 2013;26(3):123-130.
24. Fleming J, Bailey DL, Chan HK, Conway J, Kuehl PJ, Laube BL, Newman S. Standardization of techniques for using single-photon emission computed tomography (SPECT) for aerosol deposition assessment of orally inhaled products. J Aerosol Med Pulm Drug Deliv 2012;25(Suppl 1):S29-S51.
25. Dolovich MB, Bailey DL. Positron emission tomography (PET) for assessing aerosol deposition of orally inhaled drug products. J Aerosol Med Pulm Drug Deliv 2012;25(Suppl 1):S52-S71.
26. Dolovich MB. ^{18}F-fluorodeoxyglucose positron emission tomographic imaging of pulmonary functions, pathology, and drug delivery. Proc Am Thorac Soc 2009;6(5):477-485.
27. van der Veldt AA, Smit EF, Lammertsma AA. Positron emission tomography as a method for measuring drug delivery to tumors in vivo: the example of [^{11}C]docetaxel. Front Oncol 2013;3:208.
28. Gorkem SB, Coskun A, Yikilmaz A, Zurakowski D, Mulkern RV, Lee EY. Evaluation of pediatric thoracic disorders: comparison of unenhanced fast-imaging-sequence 1.5-T MRI and contrast-enhanced MDCT. AJR 2013;200(6):1352-1357.
29. Thompson RB, Finlay WH. Using MRI to measure aerosol deposition. J Aerosol Med Pulm Drug Deliv 2012;25(2):55-62.
30. Laube BL, Corcoran TE, Devadason SG, Dolovich MB, Fleming J, Newman S. Editorial: standards for lung imaging techniques. J Aerosol Med Pulm Drug Deliv 2012;25(Suppl 1):S1-S2.
31. Donaldson SH, Bennett WD, Zeman KL, Knowles MR, Tarran R, Boucher RC. Mucus clearance and lung function in cystic fibrosis with hypertonic saline. N Engl J Med 2006;354(3):241-250.
32. Donaldson SH, Corcoran TE, Laube BL, Bennett WD. Mucociliary clearance as an outcome measure for cystic fibrosis clinical research. Proc Am Thorac Soc 2007;4(4):399-405.
33. Robinson M, Eberl S, Tomlinson C, Daviskas E, Regnis JA, Bailey DL, et al. Regional mucociliary clearance in patients with cystic fibrosis. J Aerosol Med 2000;13(2):73-86.
34. Nolop KB, Maxwell DL, Fleming JS, Braude S, Hughes JM, Royston D. A comparison of ^{99m}Tc-DTPA and ^{113m}In-DTPA aerosol clearances in humans. Effects of smoking, hyperinflation, and in vitro oxidation. Am Rev Respir Dis 1987;136(5):1112-1116.
35. Ilowite JS, Bennett WD, Sheetz MS, Groth ML, Nierman DM. Permeability of the bronchial mucosa to ^{99m}Tc-DTPA in asthma. Am Rev Respir Dis 1989;139(5):1139-1143.
36. Corcoran TE, Thomas KM, Brown S, Myerburg MM, Locke LW, Pilewski JM. Liquid hyper-absorption as a cause of increased DTPA clearance in the cystic fibrosis airway. EJNMMI Res 2013;3(1):14.
37. Locke LW, Myerburg MM, Markovetz MR, Parker RS, Weber L, Czachowski MR, et al. Quantitative imaging of airway liquid absorption in cystic fibrosis. Eur Respir J 2014;44(3):675-684.
38. Beer AJ, Grosu AL, Carlsen J, Kolk A, Sarbia M, Stangier I, et al. [^{18}F]Galacto-RGD positron emission tomography for imaging of $\alpha5\beta3$ expression on the neovasculature in patients with squamous cell carcinoma of the head and neck. Clin Cancer Res 2007;13(22):6610-6616.
39. Gupta NC, Rogers JS, Graeber GM, Gregory JL, Waheed U, Mullet D, Atkins M. Clinical role of F-18 fluorodeoxyglucose positron emission tomography imaging in patients with lung cancer and suspected malignant pleural effusion. Chest 2002;122(6):1918-1924.
40. Jones HA, Donovan T, Goddard MJ, McNeil K, Atkinson C, Clark JC, et al. Use of 18FDG-pet to discriminate between infection and rejection in lung transplant recipients. Transplantation 2004;77(9): 1462-1464.
41. de Prost N, Tucci MR, Melo MF. Assessment of lung inflammation with ^{18}F-FDG PET during acute lung injury. AJR 2010;195(2):292-300.
42. Venegas J, Winkler T, Harris RS. Lung physiology and aerosol deposition imaged with positron emission tomography. J Aerosol Med Pulm Drug Deliv 2013;26(1):1-8.
43. Lee CU, White DB, Sykes AM. Establishing a chest MRI practice and its clinical applications: our insight and protocols. J Clin Imaging Sci 2014;4:17.

Discussion

Rubin: Tim, that was great. I'm particularly excited about the comparison between absorption and mucus clearance. That is so powerful for our understanding of the physiology. When is it going to be ready for prime time?

Corcoran: We published an imaging study,[1] and we published a lot of the background work as well.[2] I think it's important; it's a tough case to make unless you look at the cell work, and frankly, I know people aren't generally as interested in that. But we did a lot of mechanistic work to show that

our imaging is really showing us something about absorption through the epithelium. Taken together, I think we have a pretty good case out there in the literature now. We have had some interest from folks who are trying to develop therapies to add this to what they're doing clinically.

Berlinski: Can you comment about the repeatability of the studies? You're doing these imaging studies, and like any test that we use, we always struggle with some of the outcomes because they're not very repeatable.

Corcoran: Absolutely. We have a study under way right now looking at the repeatability, just doing 2 measurements in CF [cystic fibrosis] subjects within a few weeks of each other and looking at the repeatability of mucus clearance and absorption. That should be finished within the next month or so.

Hill: Thanks for that very elegant presentation. One of the things that was striking about the deposition studies you showed was the heterogeneity in a lot of these patients, especially after transplantation; it's really striking. I'm wondering, have you been able to think about correlating this with efficacy of medications? You can imagine—and I was actually going to ask Marcos [Restrepo] this when he gave his talk—that antibiotics or cyclosporine, for example, might depend on how well distributed the drug is in the lung.

Corcoran: It's like I said, it's like getting a 2- or 3-fold difference in an oral medication; you would think to yourself that it's obviously going to make a difference in your outcome. The limited evidence we have is what I've put up there. When we were able to measure these doses early in a trial,[3] there was a relationship between what the subject got into the right part of the lung, which in this case was the periphery, and the change in pulmonary function they got out of it over time. I don't know whether many big clinical studies have included measurement of dosing. I suspect that with many drugs, if they had looked at that early on, 1) they might have tried harder to get the dosing to be what they wanted it to be, and 2) they might have seen a relationship between dose and effect. It just makes sense that you should because if the drug's not getting to where you want it to be, there's no way it can work.

Hill: Marcos, do you have any comments?

Restrepo: There's a very nice study you should review by Lu et al.[4] They did CT [computed tomography] scans after administration of ceftazidime, and they showed how it really concentrated in different parts of the lung in different time frames and different dates. And I agree with Tim that the correlation is really variable, but it's good in certain medications. It cannot be extrapolated to every medication that gets aerosolized. I don't know the data on many different antibiotics because I think that, with these novel experiments, there are not very many in the literature to my knowledge.

Hess: I think my question follows this: there's a paper[5] I will present tomorrow morning from a group who enrolled subjects with severe acute asthma and delivered radioisotope-tagged albuterol. The subjects were randomized into a nebulizer group who took it the usual way and a group who had the nebulizer in line with NIV [noninvasive ventilation]. They showed no difference in deposition or clearance between the 2 groups, but impressive differences in spirometry. I've been struggling as to how I will explain that. Maybe you can help me?

Corcoran: I brought up some of the issues we have with trying to quantify dose within the lungs, and you have to wonder if there is one treatment reaching more of the small airways, maybe a larger portion is in the medium airways. We just don't have a way to show that through these techniques. I think we're finding our limits with these techniques and reaching out to try and do things like co-register an anatomical image along with the deposition image and getting into 3D so we can really get a better idea as to what portion of the lung we're reaching. Lung dosing is probably not the story; it's dose in different areas, dose in the periphery. That would be my thought, that we're probably trying to apply a coarse technique, and it's the finer differences in deposition that really matter. That's a very interesting study.

O'Malley: I'm so curious, Dean. Which group did better in spirometry?

Hess: The group who got their albuterol bronchodilator with NIV did better.

‡ **Suggett:** Nice talk, Tim. I just wonder if you would comment on the applicability of hyperpolarized helium and imaging?

Corcoran: Hyperpolarized helium—my understanding of this is fairly limited—is that it's a ventilation technique. Correct? So you're able to use the hyperpolarized helium to get a better illustration of where air ventilation is going. You would assume that there would be a nice relationship between where ventilation is and where aerosol is, but I haven't seen it used along with an aerosol technique. I may just be missing it in the literature.

‡ **Suggett:** No, I haven't either. I've seen it when looking at airway ventilation, but I wonder if it could be used after giving a drug just to see the effect.

Corcoran: I'm a big fan of trying to get a couple things out of a study; if you can image physiology and drug deposition together, I think there's a lot more information in that than imaging them separately. Imaging disease using nuclear techniques is entirely possible now; we could think about trying to image sites of disease in the lung and then give the drug and see how much of the drug is actually finding its way to the sites of disease. For example, a marker of inflammation you could see on an image like this would be great. They do exist, and then maybe you come along after the inflammation and give the drug and see if the drug is going to the disease. I think the future will be adding these techniques together.

‡ **Suggett:** Even looking to mucus clearance, if you're trying to identify where clearance is needed in the lungs, it might become clearer if mucus plugs were linked to resultant impacts on lung ventilation.

Corcoran: Yes, and linking nuclear scans with anatomical scans is very doable now.

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REFERENCES

1. Locke LW, Myerburg MM, Markovetz MR, Parker RS, Weber L, Czachowski MR, et al. Quantitative imaging of airway liquid absorption in cystic fibrosis. Eur Respir J 2014;44(3):675-684.
2. Corcoran TE, Thomas KM, Brown S, Myerburg MM, Locke LW, Pilewski JM. Liquid hyper-absorption as a cause of increased DTPA clearance in the cystic fibrosis airway. EJNMMI Res 2013;3(1):14.
3. Corcoran TE, Smaldone GC, Dauber JH, Smith DA, McCurry KR, Burckart GJ, et al. Preservation of post-transplant lung function with aerosol cyclosporine. Eur Respir J 2004;23(3):378-383.
4. Lu Q, Yang J, Liu Z, Gutierrez C, Aymard G, Rouby JJ; Nebulized Antibiotics Study Group. Nebulized ceftazidime and amikacin in ventilator-associated pneumonia caused by *Pseudomonas aeruginosa.* Am J Respir Crit Care Med 2011;184(1):106-115.
5. Galindo-Filho VC, Brandao DC, Ferreira Rde C, Menezes MJ, Almeida-Filho P, Parreira VF, et al. Noninvasive ventilation coupled with nebulization during asthma crises: a randomized controlled trial. Respir Care 2013;58(2):241-249.