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EDITORIAL

Lung pathology and imaging

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Perspective

Fifty years ago, Dr. Leonard Freeman—then a fledgling radiology resident and now the senior author of one of the reviews in this issue—attended a weekend course to learn about a new discipline called nuclear medicine.

At the course, he saw something he had never witnessed previously: images of lung perfusion. This new technique was presented by Dr. James Quinn and Dr. Henry Wagner, two of the pioneers of this field. Lung perfusion imaging was not yet an FDA-approved procedure, but with Dr. Quinn's help young Dr. Freeman was able to obtain, from E. R. Squibb Pharmaceuticals, the I-131 macroaggregated albumin (MAA) radiopharmaceutical that was being used to image lung perfusion. He started performing studies and was able to validate and correlate the results with pulmonary angiograms. This was to be the topic of his first presentation at the Society of Nuclear Medicine meeting in June 1967, which paved the way for the publication, the following year, of an early paper on the subject [1]. Needless to say, a young clinical investigator would face substantially greater bureaucratic hurdles today!

This issue of *Clinical and Translational Imaging* illustrates the progress that has been made in nuclear medicine and molecular imaging of the lung in the ensuing half-century, despite the attentions of regulators, administrators and politicians worldwide. The articles in this issue demonstrate the proliferation of radiopharmaceuticals and the sophistication of the instrumentation that can be used to apply imaging to clinical problems and physiologic investigations in the lung. They also provide an illustration of the continued work being done to solve a number of problems that have remained unresolved despite the past half-century of work by many groups around the world. We would characterize these remaining problems in a few groups, as follows.

First, the temporal and spatial limits of signal capture remain problematic for study of regional processes in the lung, whether the process of interest is perfusion defects or enzyme activity.

Second, quantification remains unsatisfactory. It is easier with PET than with SPECT, easier with CT than with MR, and better with tomographic than with planar imaging, but it is still not good enough for many needs.

Third, there are still relatively few available radiolabeled probes. Although one can measure gross perfusion, glucose uptake and so forth, these are quite simplistic parameters. Furthermore, physiologic functions such as mucociliary clearance and endothelial clearance are still relatively inaccessible. Finally, agents that logically combine imaging with therapy are scarcely available.

Fourth, the clinical research that delineates the effectiveness, efficiency and economic value of our testing is still a patchwork of incompatible methods and fragmentary results.

For this issue of the journal, we have chosen contributions that are able to reflect the progress and problems in these areas, with specific reference to pulmonary embolism (PE) and pulmonary pathophysiology.

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Imaging of pulmonary embolism

One of the main applications of lung imaging has been the diagnosis, follow-up and physiologic monitoring of PE. Accordingly, the first group of articles in this issue evaluates the progress that is being made toward solving the persistent issues of the effectiveness, efficiency and, by implication, economic value of the ways in which we perform and interpret scintigraphy for PE.

The pathophysiologic mechanisms underlying the clinical presentation of PE and their relationship with the practical application of lung scintigraphy (V/Q or Q scanning?) for the diagnosis of the disease are the main focus of the review by Dr. Palla and colleagues, who present the clinical experience in PE gathered at the University of Pisa over the last 20 years.

Another main area of interest in the imaging of PE is the use of the ventilation–perfusion (VQ) scan in patients with suspected disease. Various research groups have made signal contributions to this area of study, but the vast continuing experience of Dr. Freeman and colleagues at the Montefiore Medical Center places them among the perennial leaders. Therefore, their review, in which they present their continued accumulation and analysis of clinical research experience with the VQ scan in such patients, and the role and methods of VQ scanning, deserves particular attention.

A study of the use of scintigraphy in PE is provided by Dr. Stein and colleagues in a paper that updates a previous systematic review by some of the same authors [2]. They focus on published results of the use of SPECT instrumentation in suspected PE and find that, by and large, the clinical research methods used to investigate the accuracy of SPECT do not fulfill contemporary standards for clinical trials of diagnostic test accuracy. We expect that this conclusion will occasion some comment from proponents of SPECT, although we emphasize that we do not equate this result with a recommendation not to use SPECT.

The final perspective on contemporary PE imaging comes from Dr. Sardanelli and Dr. Sostman, who evaluate the current and future prospects for MR imaging of PE. This is an important consideration, since in many clinical practices today, scintigraphy is more competitive with MR than with CT.

Lung function and molecular physiology

The study of lung function and molecular physiology with imaging is as venerable a topic as the evaluation of suspected PE, but it has acquired new momentum under its new "branding" as molecular imaging and (more importantly), with the availability of better molecular probes and signal capturing methods. The second group of articles in this issue reveals the stunning progress that has been made over the past few decades in the areas of instrumentation, radiopharmaceuticals and applications in the study of pathophysiology. These papers illustrate responses to current limitations in resolution, quantification and probe development.

It is axiomatic that imaging of lung pathophysiology cannot be better than the ability to quantify the spatial and temporal distributions of radiopharmaceuticals. Accordingly, attenuation and motion correction have been important venues of technical development of PET and SPECT; Dr. Chen and Dr. Kinahan, in their review, provide an excellent illustration, through clinical examples, of how the addition of CT and MR has helped and hindered these developments.

Although the most common application of radiolabeled aerosols for imaging of the lungs is for ventilation scintigraphy as a component of VQ scanning for the diagnosis of PE, radiolabeled aerosols have been used for a number of other purposes. These include basic studies of airway pathophysiology, assessment of the deposition of pharmaceutical aerosols, measurement of mucociliary clearance and assessment of the permeability of the alveolar–capillary barrier. Dr. Wollmer focuses in particular on the use of radiolabeled aerosols in chronic obstructive pulmonary disease and asthma.

Molecular imaging of the pulmonary circulation may have a role to play as a way of approaching early diagnosis of pulmonary vascular disease (particularly type 1 pulmonary hypertension), through the development of probes that target specific endothelial markers. This issue is discussed by Dr. Dupuis and colleagues. Although such probes are not near clinical use, the targets are well described and the opportunity is clear.

Finally, the use of nanoscale constructs for the diagnosis and treatment (theranosis) of lung cancer and pulmonary metastases is the topic covered by Dr. Decuzzi, Dr. Ferrari and co-authors. In addition to advancing general considerations that advocate the use of nanoconstructs, they review examples of three types of nanoparticles that could be used for MR and PET imaging in pulmonary tumors.

Summary comment

The articles in this issue provide a photograph of the present state of the art in this field and an overview of the available techniques, showing clearly how far we have traveled along the path to the future. In fact, the progress made in the use of nuclear medicine and molecular imaging techniques in the lung has been so prolific that that this

issue does not have room to accommodate all of it. The applications of PET and the full extent of oncology applications will have to await a future issue of the journal.

We hope that this issue will have practical value in daily practice and also prompt creative thought about the possibilities offered by the techniques reviewed herein. The problems have been attacked but not defeated.

Conflict of interest Massimo Pistolesi and Dirk Sostman declare no conflict of interest

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