Perspectives in Nuclear Medicine: Pulmonary Studies

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Since the introduction of I-131 labeled macroaggregates in 1964 (1), noninvasive techniques involving injections of radiolabeled agents and remote detection of emitted radiation have become well established in detecting pulmonary disorders in routine clinical medicine. In the past, pulmonary nuclear medicine has been dominated by studies that depict the distribution of pulmonary perfusion and/or ventilation-perfusion balance (e.g., for the detection of pulmonary embolism, obstructive airway disease, lung carcinoma). With the recent development of emission tomography and the potential for new, function-oriented radiopharmaceuticals, however, pulmonary nuclear medicine is entering a new era. We review briefly the status of contemporary pulmonary nuclear medicine in several areas of major interest and applications and focus on areas where new developments are needed and seem feasible in the near future. Several important regional physiological processes measurable by these techniques include: (a) the presence or absence of pulmonary embolism, (b) relative pulmonary blood flow, (c) permeability to specific molecules, (d) lung tissue metabolism, (e) ventilation distribution, and (f) the relationship between ventilation and blood flow (perfusion).

The physical parameters actually measured in radionuclide emission studies are the temporal and spatial relations of the distribution of tracer in the lungs after inhalation or peripheral injection. If the tracer is a diffusible substrate, the time rate of change can reflect transit time through various regions of the lung. If the tracer is on macroaggregates or microspheres, the amount lodging in any portion of the lung after peripheral injection can be related to relative flow in the lung. Tracers that are diffusible will wash into and out of the lungs at a rate proportional not only to flow but also to membrane permeability. Metabolism of the lung is reflected by the rate of extraction and disappearance of various labeled radiopharmaceuticals.

Generally, a gamma camera is used to acquire four to eight views of the distribution of the radionuclide after inhalation or injection. Recently, however, positron emission tomography has been applied to quantitative studies of perfusion and distribution of lung water.

STATE OF KNOWLEDGE AND TECHNOLOGY

Pulmonary embolism. It has been estimated that there are over 600,000 new cases of pulmonary embolism in the United States each year (2), and that as many as 75% of these lack a correct diagnosis. Because the mortality for untreated pulmonary embolism is estimated to be about 30%, there is an important emphasis on noninvasive methods for the diagnosis of this condition. Nuclear medicine imaging techniques provide a method for the differentiation of pulmonary embolism from other pulmonary conditions, such as pneumonia, atelectasis, chronic obstructive pulmonary disease, pleuritis, etc. Initially, regional pulmonary perfusion was evaluated using I-131 labeled biodegradable macroaggregates and gamma camera imaging instruments (1,3). This method was found to be extremely sensitive in detecting perfusion defects. However, because of the large number of nonembolic causes of decreased perfusion (e.g., increased vascular resistance, external compression, bronchial constriction, etc.), perfusion studies alone were not specific for pulmonary embolism (4). Attempts to increase the specificity of scintigraphic diagnosis of pulmonary embolism have led to the development of pulmonary ventilation studies using radioactive gases such as xenon-133, xenon-127, krypton-81m, a number of...
TABLE 1. PROBABILISTIC ESTIMATES OF PULMONARY EMBOLISM, P(PE | S), IN THREE CLINICAL SITUATIONS ASSOCIATED WITH SELECTED SCINTIGRAPHIC OUTCOMES

<table>
<thead>
<tr>
<th>Scan pattern</th>
<th>Posterior probabilities for clinical chances of pulmonary embolism</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>0.04</td>
</tr>
<tr>
<td>Many perfusion defects, no ventilation study</td>
<td></td>
</tr>
<tr>
<td>Subsegmental</td>
<td>0.01</td>
</tr>
<tr>
<td>Segmental</td>
<td>0.10*</td>
</tr>
<tr>
<td>Lobar</td>
<td>0.26*</td>
</tr>
<tr>
<td>Many perfusion defects, V/Q mismatch</td>
<td></td>
</tr>
<tr>
<td>Lobar/segmental</td>
<td>0.54*</td>
</tr>
<tr>
<td>Subsegmental</td>
<td>0.01</td>
</tr>
<tr>
<td>Many perfusion defects, any size and V/Q match</td>
<td>0</td>
</tr>
</tbody>
</table>

* Probabilistic estimates in intermediate range.
† This table originally appeared as Table 4 of Ref. 8, p 322.

aerosols, and more recently, positron-emitting agents such as labeled carbon dioxide. The combination of both ventilation and perfusion studies with multiple views has resulted in over 90% true-negative diagnosis and has reduced the high false-positive rate in the diagnosis of pulmonary embolism.

The reliability of perfusion or ventilation-perfusion studies in the diagnosis of pulmonary embolism has been studied by a number of investigators over the past 5 yr (5–12). In general, if a perfusion scan is entirely normal, no clinically significant pulmonary embolism exists. It is generally agreed that ventilation-perfusion studies showing normal ventilation with large perfusion defects are almost invariably diagnostic of pulmonary embolism. That is, ventilation-perfusion mismatch correlates to a high degree with pulmonary embolism as detected by conventional angiography. However, the proper role of ventilation-perfusion studies and subsequent angiography depends not only upon the scintigraphic patterns or degree of ventilation-perfusion mismatch, but also on the disease prevalence or suspicion level before these examinations are performed. This disease prevalence, also called the prior probability when applied to a particular patient, is an extremely important factor in the interpretation of lung scans. The probability that a patient has pulmonary embolism depends on the particular scan pattern for which the sensitivity and specificity figures were derived as well as the prior probability that pulmonary embolism might exist in that patient. This point can be understood from Bayes' theorem:

Probability of having pulmonary embolism

\[
\frac{1}{1 + \frac{\text{False positive of test}}{\text{True positive of test}} \times \frac{\text{Incidence of no P.E.}}{\text{Incidence of P.E.}}}
\]

This method of presenting Bayes' theorem shows that the prior probability of pulmonary embolism in a particular patient is as important as the sensitivity and specificity figures (true-positives and false-positives) for a particular ventilation-perfusion pattern. Clearly, the lower the ratio of false-positive to true-positive for a particular scan pattern, the greater the certainty that pulmonary embolism exists in a patient with the particular scan pattern. In this case, a scan pattern might contain many defects, segmental in size or larger; or a single segmental defect with a ventilation-perfusion mismatch; or many defects subsegmental in size with normal ventilation, etc. Some scintigraphic patterns have such a high true-positive/false-positive ratio (likelihood ratio) that the probability a particular patient will have pulmonary embolism is very high. Other patterns with lower likelihood ratios depend heavily upon disease prevalence for establishing the diagnosis of pulmonary embolism with a high degree of reliability. Table 1 describes how for various ventilation-perfusion patterns the likelihood ratios interact with prior probabilities to give posterior probabilities for pulmonary embolism in patients suspected of having this disease.

Controversies have arisen during the past few years regarding the under- and over-diagnosis of pulmonary embolism using nuclear medicine techniques (13). A major issue in these controversies is that no valid information is available on prevalence data for use in the above equation. A number of studies have given similar likelihood ratios for particular patterns, but they are not able to provide prevalence data because of selection biases involved in decisions to perform a ventilation-perfusion study and then an angiogram. In addition, there have been no studies capable of developing a predictive score or an index giving the probability that a particular patient is likely to have pulmonary embolism on the basis of his presenting factors. Such data are available for patients suspected of having coronary artery
disease and it is hoped that with larger data bases, such information might become available for pulmonary embolism as well. The lack of these data prevents making a sound estimate of the prior probability of pulmonary embolism in a particular patient or in particular classes of patients. Without this, the accuracy of decisions for treating pulmonary embolism immediately, or for performing angiography, is difficult to evaluate or compare from one group to another. A new approach to the problem of detecting pulmonary embolism involves the use of positron emission tomography after inhalation of radioactive C\textsuperscript{15}O\textsubscript{2} and \textsuperscript{11}CO (14–17) or injection of perfusion indicators such as \textsuperscript{68}Ga-EDTA (18) and generator-produced \textsuperscript{82}Rb (19). For example, radioactive CO\textsubscript{2} is retained in pulmonary blood distal to the embolic obstruction and appears as an area of increased radioactivity that delineates the size and magnitude of the affected zone (14–17). This technique differs fundamentally from the conventional perfusion lung scan with \textsuperscript{99m}Tc-labeled albumin microspheres in that pulmonary capillary blood is labeled with a soluble radioactive gas. The technique is based on the formation of radioactive water when the C\textsuperscript{15}O\textsubscript{2} is converted by carbonic anhydrase in pulmonary erythrocytes to \textsuperscript{15}O\textsubscript{2}-labeled water. The embolized zones in animals have been shown to have a slower washout than that in normal zones and reveal the presence of pulmonary embolism. Note that this technique measures some complex, as yet undefined, function of pulmonary water space, pulmonary blood flow, and vascular recirculation.

A third approach using generator-produced \textsuperscript{68}Ga and \textsuperscript{82}Rb involves the first-pass detection of relative mean transit times for perfusion and the study of permeability by the accumulation of such nuclides as \textsuperscript{82}Rb\textsuperscript{+}, \textsuperscript{68}Ga-EDTA, or \textsuperscript{68}Ga-transferrin in lung parenchyma (18,19). The promise of emission tomography as a practical clinical technique awaits solution to problems of attenuation compensation, lung motion, and the need for multiple-section tomographs of high sensitivity. Because positron emitters available from generators have a potential role in pulmonary disease studies, the future is not necessarily limited to the availability of cyclotrons.

A promising recent approach to positive identification of fresh pulmonary emboli is the use of In-111-labeled platelets. However, it appears that this method is limited to detection of early embolism or fresh emboli in patients not on heparin (20–22).

Lung water. In the area of pulmonary water detection, there is a need for new procedures, not only for the gross detection of local density changes, but also for the characterization of changes in compartment size. Invasive techniques have been developed to explore compartment sizes and exchange rates in periarterial spaces, alveolar-venule spaces, and bronchovesicular spaces. These invasive techniques have been promoted to measure filtration and reflection coefficients by examination of arterial-to-venous differences and plasma-to-lymph concentration ratios for the injected material. There is no technique, at present, for measuring microvascular pulmonary membrane transport by noninvasive methods.

An important concept in the development of techniques for measuring the distribution of lung water is the fact that lung water can exist in any number of compartments from the bronchovesicular space to the alveolar spaces. Proton nuclear magnetic resonance will probably be the method of choice for measurement of lung water.

Lung permeability and fluid balance. Permeability to specific molecules has until recently been a field limited to invasive techniques. By using clearance observations with aerosols of diethylene-triaminepenta-acetic acid (DTPA) and conventional instrumentation (12), or other molecules and positron emission tomography, it is possible to evaluate some features of membrane transport.

Physiological investigation of lung fluid balance with invasive techniques has progressed to the following three frontiers: (a) attempts to identify specific relationships between the flow of fluid across the microvascular surface and the flow of lymphatic fluid draining the lung interstitium and other adjacent tissue; (b) attempts to characterize the compartments of the interstitial fluid space; and (c) attempts to measure the physical properties of the microvascular environment (compliance of the interstitial space, and interstitial and microvascular pressures). Noninvasive techniques will have difficulty competing with these methods. To establish rate constants, observations of tracer clearance must be supplemented by measures of regional perfusion and vascular volume. At present, it is not clear how the convective and diffusive components of lung membrane transport of macromolecules can be separated by noninvasive techniques.

Mucociliary clearance. Nuclear medicine techniques provide potentially powerful methods for the evaluation of mucociliary clearance in health and disease. The basic procedure involves the inhalation of inert radioaerosols of various particle sizes and the evaluation of their clearance by means of serial images (23,24).

Metabolism of lung tissues and vessels. Metabolism encompasses a broad spectrum of possibilities for fundamental physiological studies as well as others that might lend themselves to differential diagnosis in clinical problems—particularly some psychoses that might be associated with abnormal lung metabolism of bioamines. In addition to its main function as an organ of external gas exchange, the lung serves as the metabolic regulator of substances circulating in the blood, somewhat analogous to the major role of the kidney (25). The lung has been shown to modify many circulating vasoactive
substances either by activation, inactivation, or removal and storage for subsequent metabolism and release (26, 27). The relation of the pulmonary kinetics of 5-hydroxytryptamine and norepinephrine removal in man to specific disease entities, not only of the lung but elsewhere in the body, has not been defined, primarily because until recently such studies have been invasive. In the past few years, however, the uptake of bioamines (28–30) and the kinetics of psychoactive compounds such as chlorpromazine (31) have been imaged in the lung. Kinetic studies have been pursued using octylamine hydrochloride labeled with carbon-11 and 5-hydroxytryptamine labeled with carbon-11 (32). Apparently the amines bind to high-affinity sites located on the membranes of pulmonary endothelial cells. With the advent of positron emission tomography, it is possible to quantitate the uptake and clearance of bioamines by labeling them with carbon-11. This new approach presents the potential of examining the efficiency whereby monoamine oxidase activity controls the circulating levels of compounds such as serotonin and norepinephrine. For example, the capability of monoamine oxidase inhibitors to alter the biodistribution and clearance of these monoamines can be studied. To what extent such studies will be important for pulmonary physiology in and of itself has yet to be ascertained, but it seems very likely that the investigation of the regulatory function of the lungs will provide insights into a number of pulmonary and nonpulmonary diseases.

THE FUTURE

Significant new areas of research with high potential for important clinical applications in radiotracer lung studies are likely to occur in the areas of lung water determination, permeability changes associated with disease, investigation of the immune system, and investigations of the metabolic function of the lung as a regulator of circulating bioamines in man. These areas of research and development have their bases in the development of new methods of emission tomography for quantitative estimation of the distribution of tracers labeled with positron or single-photon emitters, and development of new chemical methods for labeling organic compounds.

The basic problems associated with future studies aimed at assessing the value of ventilation-perfusion scans for the diagnosis of pulmonary embolism reside not only with improving specificity, but also with better estimates of the prior probability of pulmonary embolism in the patient being evaluated. In addition, the instrumentation and procedures for assessing ventilation and perfusion vary widely from center to center and must become more standardized. Well-defined diagnostic criteria (7) and a uniform diagnostic algorithm (33) are the key elements for reducing the variability in ventilation-perfusion image interpretation. In the past few years, there has been a consolidation of knowledge and a perfection of methods in some centers. Further standardization of this sort is needed. There is a possibility that pulmonary embolism will be detected with improved sensitivity and specificity using emission tomography. Comparative studies with standard ventilation-perfusion imaging require appropriate emission tomography instrumentation that will give fully three-dimensional images of the distribution of tracer in the lung.

Specific areas for new research activities include:

(1) Analysis of the metabolic function of the lung, especially the lung's effect on the concentration of circulating bioamines and other substances, is an important category for new research. In order for sound research to be pursued, it is important that the specific activity of the prepared radiopharmaceuticals be sufficiently high to allow studies to proceed without the indeterminant error of receptor-site saturation. In addition, it is necessary to measure to what extent the label on a particular organic compound would be metabolized and redistributed in the tissues. Animal models seem to be indicated, even to the extent of performing autoradiography and microanalytical chemistry to trace the fate of labels in these basic studies of lung metabolism. There is sufficient information with regard to the fate of some radiotracers to warrant human investigation of metabolic behavior of amino acids, bioamines, and other compounds in normal persons and in patients with pulmonary disease.

(2) Development of emission tomographic techniques for the lung. These techniques will be needed for any studies of positron emitters in the lung and can also be used for evaluating regional ventilation-perfusion balance and other parameters that can be evaluated by gamma-emitting radionuclides. Instrumentation that allows simultaneous evaluation of several lung levels by tomography is needed. In addition, electrical (e.g., gating) or physiological methods for reducing the effects of lung motion on the information derived by emission tomography are needed. Animal studies will probably provide the initial data base for these efforts.

(3) Assessment of pulmonary fluid balance, i.e., pulmonary water and perfusion, vascular permeability, and other physiologic parameters. These studies require maneuvers that will allow one to extract the perfusion and permeability influences from the time-activity changes in the lung. Physiologic parameters of regional lung-fluid balance that remain to be quantitated noninvasively include large-vessel and microvascular volumes; interstitial fluid volumes; arterial microvascular and interstitial pressures, and microvascular and alveolar membrane transport parameters. Transport parameters such as reflection coefficients and permeability of macromolecules are not separable by known noninvasive methods. Tomography using positron emitters can pro-
vide estimates of the net transit time and residue function for various molecules. Transmission computed tomography with contrast enhancement will delineate pulmonary vascular structures with better spatial resolution than that obtainable with emission tomography. Investigation of pulmonary exchange rates requires the development of radiolabeled substances with half-lives commensurate with the transport rates to be measured.

(4) Development of digital processing techniques for the evaluation of sequential changes in ventilation and perfusion from two-dimensional projection images. Computer-assisted scintigraphic imaging of the dynamic function of the lungs is a relatively new area. The technique is likely to add new physiological information and involves little additional radiation risk. The clinical importance of this information has yet to be determined.

CONCLUSION

Pulmonary nuclear medicine seems ready to leave an era dominated by studies of routine ventilation-perfusion imaging in the diagnosis of pulmonary embolism and to enter an era that will emphasize tomographic imaging, pulmonary dynamics, fluid balance, and metabolism. The resultant new techniques and insights should improve our understanding of many pulmonary diseases.

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REFERENCES


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12th Annual Meeting
Mid Eastern Chapter
Society of Nuclear Medicine

April 2-3, 1982
Sheraton Inn and Conference Center Fredericksburg, Virginia

Announcement and Call for Abstracts

The Scientific Program Committee of the Mid Eastern Chapter solicits the submission of abstracts from members and nonmembers of the Society of Nuclear Medicine for the 12th Annual Meeting to be held April 2-3, 1982 at Sheraton Inn and Conference Center, Fredericksburg, Virginia. Papers on all aspects of in vitro and in vivo procedures, radiopharmaceuticals, and radionuclide therapy will be considered. Abstracts should not exceed 200 words and should contain a statement of purpose, the method used, results, and conclusion. Presenting author should be underlined and his/her address enclosed.

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