EDITORIAL

Technetium-99m-DTPA Aerosol to Measure Alveolar-Capillary Membrane Permeability

The 1988 National Heart, Lung and Blood Institute (NHLBI) Workshop on Techniques to Evaluate Lung Alveolar-Microvascular Injury concluded that the rate of lung clearance of ^{99m}Tc-DTPA aerosol (DTPA) was an index of lung epithelial permeability (*1*). Increased pulmonary epithelial permeability, resulting from lung inflammation of interstitial lung disease, pneumoconioses and other causes, increases the rate of DTPA clearance. Thickening of the alveolar epithelium on the other hand reduces diffusion and therefore decreases DTPA clearance. The NHLBI Workshop concluded that DTPA clearance is a highly sensitive marker of a wide spectrum of lung insults, even those of mild degree.

A normal clearance certifies the absence of inflammation in the lung from any cause. Similarly, the rate of clearance of DTPA may be a sensitive indicator of ongoing damage in interstitial lung disease and other pathology. Assessment of DTPA clearance is a simple procedure that is exquisitely suited for the early detection of lung injury—an objective at the very core of nuclear medicine practice. Our challenge is to correlate and document alterations in DTPA clearance with specific diagnostic indices in a variety of lung diseases and, where possible, to show significant changes from the range of clearance times seen in normal control subjects. The NHLBI Workshop concluded that the information already available can be applied clinically, even though the procedure is not disease-specific.

The measurement of DTPA lung clearance for the early diagnosis of disease and for the prognosis and treatment of disease provides us with a procedure that is very sensitive, noninvasive, produces regional and global data, utilizes a readily available and relatively inexpensive tracer, is rapid to perform using standard equipment available in all clinical nuclear medicine departments and results in very low patient exposure to radiation (*2*). In comparison with ^{67}Ga imaging for pulmonary studies, measurement of DTPA clearance is faster to analyze and can be repeated at frequent intervals. However, DTPA clearance measurement is no panacea and its efficacy and limitations must be carefully determined.

In this issue of the *Journal*, Caner et al., report on the lung clearance of DTPA aerosol in diabetic patients with and without vascular complications and find that DTPA clearance of diabetics with vascular complications is significantly slower than that of diabetics without complications. DTPA clearance of the latter group was indistinguishable from that of their controls.

They suggest that the slower DTPA clearance was due to thickening of the alveolar tissue, which reduced membrane permeability. Caner et al. highlight two points: (1) the lungs may be more frequently subjected to a variety of insults ultimately causing functional impairment and pathology than previously suspected; and (2) the DTPA clearance procedure is very sensitive, demonstrating changes in pulmonary epithelial permeability that precede clinical symptoms. None of their patients had any respiratory symptoms. Caner et al.'s study should be expanded to measure the effects of medication and exercise-induced changes in DTPA clearance.

This study joins the growing list of pulmonary diseases studied by this method, since Taplin and colleagues (*3*) first successfully used inhaled aerosols for pulmonary diagnostics in the 1970s. Changes in DTPA clearance have been used to study a variety of diseases, including ARDS (*4*) and noncardiogenic pulmonary edema (*5*); asbestosis (*6*), coal workers' pneumoconiosis (*7*) and other pneumoconioses (*8*); HIV (*9*); interstitial lung diseases such as sarcoidosis (*8*), idiopathic pulmonary fibrosis (*8*), hyaline membrane disease (*10*), fibrosing alveolitis associated with systemic sclerosis (*11*) and cryptogenic fibrosing alveolitis (*11*); cigarette smoke (*12*); crack cocaine (*13*); and radiation pneumonitis (*14*). Despite these broad applications, this modality has not yet gained wide clinical acceptance.

The sensitivity of the DTPA clearance method is such that acute as well as chronic changes in lung permeability can be measured. For example, the reversibility of the effect of cigarette smoke has been well documented (*15,16*). Evidence of the reversibility of the acute inflammation in crack cocaine users has been obtained more recently (*17*). At the same time, the rate of DTPA clearance is a very sensitive indicator of ongoing damage in the lungs (*18*), as evidenced by the increased DTPA clearance of chronic users of crack cocaine (*13*). The inflammatory response in chronic crack cocaine users' lungs has also been observed in another study (*19*); all tissue specimens showed intraepithelial and submucosal inflammation. The principal uncertainty limiting its clinical usefulness is the inability to differentiate between changes in DTPA clearance due to lung injury and the contribution of other factors such as increased lung volume in noninjured lung regions and the stretching of epithelial junctions in the alveolar wall as a result of fibrotic traction (*3*) or gravity (*8*).

Other limitations include our poor understanding of the reproducibility of DTPA clearance in healthy controls

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and in patients (*20*). Well-designed systematic studies are needed in the same patient and control populations to determine the effect on DTPA clearance of such physiological factors as respiratory rate, tidal volume, FRC, and body position, so that a clinically acceptable standardized protocol can be developed. Meaningful results can be obtained from serial DTPA studies by repeating the same breathing patterns and other conditions and using each subject as his own control.

Further investigation and study of those lung diseases that result in biexponential DTPA clearance may prove fruitful. Biexponential DTPA clearance has been found in several groups, including patients with edema from ARDS (*4*), HIV infection (*9*), hyaline membrane disease (*10*) and patients without edema after exposure to coal dust (*7*) and crack cocaine (*13*). Biexponential clearance is always abnormal and indicative of greater lung injury than monoexponential clearance (*18*). This corresponds to evidence from pathologic studies of the lungs of dogs following intravenous injection of oleic acid (*21*). Biexponential clearance curves were found in studies of most smoking and ex-smoking coal miners (*7*) and crack cocaine users (*13*). In the case of neonates with hyaline membrane disease, DTPA clearance curves were biexponential shortly after birth and then changed to monoexponential curves several days later when the surfactant system became more developed.

Assessment of asymptomatic patients, which requires the use of procedures sufficiently sensitive to detect early disease, becomes very important in treating disorders like systemic sclerosis with fibrosing alveolitis (*22*). Early diagnosis results in a better response to immunosuppressive drugs, while patients with already well-established disease may fail to respond to current treatment. Harrison et al. (*22*) assessed the relative efficacy of DTPA clearance, bronchoalveolar lavage, pulmonary function measurements, chest radiographs, and histology of biopsy specimens in a group of patients. Their results indicated that CT scans, bronchoalveolar lavage, and DTPA clearance were frequently abnormal in asymptomatic patients who had normal chest radiographs. When the CT scans were normal, increased DTPA clearance and abnormal bronchoalveolar lavage had indicated lung disease in a still earlier stage. The clearance curves of all patients with abnormal chest radiographs were biexponential with fast and slow components. In 47% of the patients with normal chest radiographs, the clearance curves were also biexponential.

When conventional therapies have a high incidence of side effects, such as in fibrosing alveolitis associated with systemic sclerosis (*11,22*) and in cryptogenic fibrosing alveolitis (*11*), treatment is often delayed until symptoms have increased. By this time, considerable irreversible lung damage has often occurred.

Wells et al. (*11*) have measured DTPA clearance in a large group of patients to correctly predict progressive disease and thereby justify treatment before the patient becomes disabled. They concluded that normal DTPA clearance was indicative of stable disease, while persistently abnormal clearance identified patients at risk of deterioration.

Reduced values of pulmonary function were an inconsistent guide to prognosis and inferior to the measurement of DTPA clearance. Similarly, serial studies (*14*) are currently underway to evaluate the effects of radiation-induced lung damage on DTPA clearance in patients being treated for lung and breast carcinoma. Preliminary results show that significant changes in DTPA clearance had already occurred during the radiation treatment cycle and continued for periods up to a year. In the case of two patients who developed radiation pneumonitis, the onset of increased DTPA clearance occurred as much as six weeks before the onset of symptoms and abnormal chest radiographs. These measurements may predict trends that justify treatment of the patient while still asymptomatic and before radiographs become abnormal.

Ross et al. (*9*) used DTPA clearance to diagnose *pneumocystis carinii* pneumonia in patients with HIV. They found that the measurement of DTPA clearance was the most sensitive (92%) imaging procedure in detecting lung injury with infectious complications related to the HIV infection, especially in patients with normal chest radiographs and arterial blood gases. Imaging of ^{67}Ga lung uptake was less sensitive (74%).

Much clinical information is already available that verifies the high sensitivity of the DTPA clearance procedure in the early detection of an inflammatory lung process. Long-term studies of specific lung diseases with large patient populations are needed to compare the efficacy of DTPA clearance with other diagnostic modalities such as bronchoalveolar lavage, ^{67}Ga lung uptake and examination of biopsy specimens. The study by Caner et al. indicates that DTPA clearance also measures impairment in lung permeability that precedes clinical symptoms and other functional measurements.

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REFERENCES

1. Staub NC, Hyde RW, Crandall E. Workshop on techniques to evaluate lung alveolar-microvascular injury. *Am Rev Respir Dis* 1990;141: 1071–1077.
2. Atkins HL, Weber DA, Susskind H, et al. MIRD dose estimate report no. 16: radiation absorbed dose from technetium-99m-diethylenetriamine pentaacetic acid aerosol. *J Nucl Med* 1992;33:1717–1719.
3. Chopra SK, Taplin GV, Tashkin DP, et al. Lung clearance of soluble radioaerosols of different molecular weights in systemic sclerosis. *Thorax* 1979;34:63–67.
4. Jones JC, Minty BD, Royston D. The physiology of leaky lungs. *Br J Anaesth* 1982;54:705–721.
5. Mason GR, Effros RM, Uszler JM, et al. Small solute clearance from the lungs of patients with cardiogenic and noncardiogenic pulmonary edema. *Chest* 1985;88:327–334.
6. Gellert AR, Winter RJD, Uthayakumar S, et al. Bronchoalveolar lavage and clearance of ^{99m}Tc-DTPA in asbestosis. *Thorax* 1984;39:709.
7. Susskind H, Rom WN. Lung inflammation in coal miners assessed by uptake of ^{67}Ga-citrate and clearance of inhaled ^{99m}Tc-labeled diethyl-

enetriamine pentaacetate aerosol. *Am Rev Respir Dis* 1992;146:47–52.
8. Rinderknecht J, Shapiro L, Krauthammer M, et al. Accelerated clearance of small solvents from the lungs in interstitial lung disease. *Am Rev Respir Dis* 1980;121:105–117.
9. Rosso J, Guillon JM, Parrot A, et al. Technetium-99m-DTPA aerosol and gallium-67 scanning in pulmonary complications of human immunodeficiency virus infection. *J Nucl Med* 1992;33:81–87.
10. Jefferies AL, Coates G, O'Brodovich H. Pulmonary epithelial permeability in hyaline-membrane disease. *N Engl J Med* 1984;311:1075–1080.
11. Wells AU, Hansell DM, Harrison NK, et al. Clearance of inhaled ^{99m}Tc-DTPA predicts the clinical course of fibrosing alveolitis. *Eur Respir J* 1993;6:797–802.
12. Jones JG, Minty BD, Lawler P, et al. Increased alveolar epithelial permeability in cigarette smokers. *Lancet* 1980;1:66–68.
13. Susskind H, Weber DA, Volkow ND, et al. Increased lung permeability following long-term use of free-base cocaine (crack). *Chest* 1991; 100:903–909.
14. Susskind H, Weber DA, Lau HY, et al. Technetium-99m-DTPA lung clearance in patients with lung and breast carcinoma undergoing radiation therapy. *Am Rev Respir Dis* 1993;147: A67.
15. Mason GR, Uszler JM, Effros RM, et al. Rapidly reversible alterations of pulmonary epithelial permeability induced by smoking. *Chest* 1983;83:6–11.
16. Minty BD, Jordan C, Jones JG. Rapid improvement in abnormal pulmonary epithelial permeability after stopping cigarettes. *Br Med J* 1981; 282:1183–1186.
17. Susskind H, Weber DA, Atkins HL, et al. Does detoxification reverse the acute alveolitis of crack smokers? *J Nucl Med* 1993;34:43P.
18. Coates G, O'Brodovich H, Dolovich M. Lung clearance of ^{99m}Tc-DTPA in patients with acute lung injury and pulmonary edema. *J Thorac Imag* 1988;3:21–27.
19. Fliegiel SEG, Beals TF, Tashkin DP. Pulmonary pathology in cocaine smokers. *Am Rev Respir Dis* 1990;141:A780.
20. Smith RJ, Hyde RW, Waldman DL, et al. Effect of pattern of aerosol inhalation on clearance of technetium-99m-labeled diethylenetriamine pentaacetic acid from the lungs of normal humans. *Am Rev Respir Dis* 1992;145:1109–1116.
21. Jones JG, Minty BD, Beeley JM, et al. Pulmonary epithelial permeability is immediately increased after embolization with oleic acid but not with natural fat. *Thorax* 1982;37:169–185.
22. Harrison NK, Glanville AR, Strickland B, et al. Pulmonary involvement in systemic sclerosis: the detection of early changes by thin section CT scan, bronchoalveolar lavage and ^{99m}Tc-DTPA clearance. *Respir Med* 1989;83:403–414.