An Improved Radionuclide Technique for the Detection of Altered Pulmonary Permeability

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Technegas, an ultra-fine dry aerosol with prolonged retention in the lungs, can be modified by altering the atmosphere in which the carbon particles are generated. The modified Technegas has much faster clearance from the lung. The half-time pulmonary clearances with modified Technegas were compared to those obtained with conventional ^{99m}Tc DTPA aerosol in 50 patients. Interstitial lung disease was suspected in 12 while 38 were infected with the human immunodeficiency virus and suspected of having opportunistic lung infection. In 22 nonsmokers in whom no evidence of active pulmonary pathology was demonstrable, the mean half-time with DTPA was 52.5 min whereas the mean half-time with modified aerosol was 10.1 min. The mean half-time in 14 smokers in whom there was also no evidence of active pulmonary disease was 28.3 min with DTPA and 7.0 min with the modified method. In the 14 patients in whom altered pulmonary permeability was demonstrated by a short DTPA half-time (mean 4.8 min) there was also an accelerated half-time with modified Technegas (mean 2.5 min). It is concluded that the modified Technegas procedure offers a simple but accurate method of identifying individuals having opportunistic infection or other diffuse lung pathology.

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Alterations in the pulmonary clearance of soluble radioaerosols was first shown by Chopra et al. (*1*) to be capable of differentiating normal from abnormal lungs. As reviewed by Coates and O'Brodovich (*2*), the technique has subsequently been widely utilized since the rate at which the aerosol leaves the lungs by diffusion into the vascular space has been shown to be altered in many pulmonary disorders. The role of Technetium-99m-DTPA clearance has been evaluated in the detection of opportunistic infection in patients with the acquired immunodeficiency syndrome, in view of the effect on the integrity of the alveolar membrane. Abnormal clearance rates were demonstrated by Mason et al. (*3*), confirmed by a number of workers, including O'Doherty et al. (*4*) and ourselves (*5*). The investigation has assumed a major diagnostic role in this common disease.

Most studies of pulmonary radioaerosol clearance have employed ^{99m}Tc-DTPA aerosol, since it is a common agent for ventilation studies. However, since its introduction by Burch et al. (*6*) there has been increasing interest in the alternative use of "Technegas," an ultra-fine dispersion of ^{99m}Tc-labeled carbon particles that are produced by combustion of [^{99m}Tc]pertechnetate in a graphite crucible in an atmosphere of 100% argon. Its major advantage lies in the fact that the particle size allows good peripheral penetration with little central deposition after only 2–5 breaths. The agent has prolonged pulmonary retention, clearing from the lungs with the half-life of the radionuclide. However, lung clearance can be markedly altered by the combustion of the crucible in an atmosphere of 97% argon and 3% oxygen. With this modification, the subsequent half-clearance time of the radioactivity from the lungs in normal subjects is markedly shortened. This study has therefore been undertaken to ascertain whether this "modified" aerosol can be routinely utilized to identify altered pulmonary permeability, permitting it to be substituted for ^{99m}Tc-DTPA.

MATERIALS AND METHODS

Thirty-eight patients infected with the human immunodeficiency virus (HIV) and suspected of having opportunistic lung infection, and 12 patients with suspected idiopathic interstitial lung disease were prospectively studied. The mean age was 41 yr with a range of 23–76 yr. There were 42 males and 8 females.

All patients were studied in the Department of Nuclear Medicine using a standardized protocol after informed consent was obtained. An initial study was obtained utilizing "modified" Technegas (T-gas) and a further study with ^{99m}Tc-diethylene triamine penta acetic acid (DTPA) was performed 45–60 min later. Chest radiography, arterial blood gases, lactate dehydrogenase (LDH) levels, and sputum analysis were performed in the majority of patients thought to have opportunistic infection.

The modified T-gas was produced in the generator manufactured by Tetley Technologies, Sydney, essentially according to the method used to prepare standard Technegas. The graphite crucible was rinsed with ethyl alcohol, then loaded with 370-455MBq of [^{99m}Tc]pertechnetate in 0.1 ml. It was preheated in the sealed lead-lined chamber for 6 min to evaporate the liquid prior to combustion at 2,500 C in an atmosphere of 97% argon

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and 3% oxygen, rather than the usual atmosphere of 100% argon. Our measurements to date indicate that, immediately after generation, 80% of the particles have a mass median aerodynamic diameter (MMAD) of less than 0.1 μm. The modified Technegas was administered through a mouthpiece, with a nose clip in situ, to the patients. The patients slowly inhaled and then held their breath for 5 sec at the maximal point of inspiration. They subsequently exhaled through the mouthpiece, the sequence being repeated till the desired count rate was achieved. In the majority of patients a satisfactory count rate of 3,000 cps was achieved following 2–5 inspiratory efforts. This is equivalent to approximately 80 MBq of aerosol in the lungs. The aerosol was delivered from the sealed chamber by disposable teflon tubing with a trap for exhaled gas.

Technetium-99m-DTPA (1.5 GBq) was nebulized, using a commercially available Bennett twin nebulizer, through a customized filter to ensure uniform droplet size, allowing adequate penetration to the distal airways. The nebulized aerosol was then collected in a standard 3-litre reservoir bag for further settling out of large droplets, according to the technique described by Hayes et al. (*7*). The resultant aerosol has a MMAD of 0.7 μm and geometric standard deviation (GSD) 1.2. A one-way valve adjacent to the mouthpiece enabled the conduction of exhaled aerosol to a trap. The patient then undertook normal tidal volume respiration until a count rate of 3,000 cps was established or until 3 min had elapsed.

The modified Technegas and the aerosolized DTPA were administered in the supine position and the patients remained in this position throughout the imaging which was performed over the posterior lung fields using a large field of view gamma camera (GE 400AT) fitted with a LEAP collimator and interfaced to a computer. Counts were acquired into a 64 × 64 matrix at 30 sec. intervals for 15 min for the T-gas study and 30 min for the DTPA study. There was a 45-min delay between the two studies and the second study was commenced 10 min prior to DTPA administration to allow correction for residual T-gas activity.

Time-activity curves were obtained for each whole lung. The lung-activity curves were then corrected for area normalized background activity using a region drawn over the shoulders. The contribution to each DTPA study arising from residual pulmonary activity due to a prior T-gas study was estimated by extrapolation of a single exponential fitted to the 10-min of data acquired over each lung before DTPA administration. DTPA lung activity curves were then corrected by subtraction of this estimate.

The corrected whole lung curves were then inspected for evidence of an initial rapid phase, with cursors placed at the peak and the 7-min mark. A least squares single exponential fit was applied to data between the cursors. A time to half clearance was obtained for this initial phase.

If the corrected whole lung curve data appeared curved when displayed on a semi-log plot, it was assumed to be a sum of two exponentials. A fit to the final 5 min of data was thus applied to estimate the slower exponential, which was then subtracted away, leaving data on which a fit for the fast exponential was performed and a time to half-clearance similarly calculated.

RESULTS

Times to half-clearance ($T_{1/2}$) were obtained in 22 nonsmokers with no evidence of active pulmonary pathology (Table 1). These values ranged from 19.8 to 132.4 min. (mean = 52.5, s.d. = 29.5) for ^{99m}Tc-DTPA and in the corresponding T-gas studies from 6.8 to 16.7 min (mean = 10.1, s.d. = 2.4). The range in 14 smokers, in whom there was also no evidence of active pulmonary disease, was 10.0 to 42.0 min (mean = 28.3, s.d. = 15.6) for ^{99m}Tc-DTPA and in the T-gas studies 5.7 to 9.0 min (mean = 7.0, s.d. = 1.1). All clearance curves in both the normal smokers and nonsmokers were monophasic.

Lung clearance was judged to be abnormal dependent on the DTPA aerosol lung clearance curve shape and the value of the half-clearance time. In 14 patients, 7 of whom were smokers, there were markedly accelerated half-clearance times with biexponential clearance curves. *Pneumocystis carinii* pneumonia (PCP) was diagnosed in 8 patients, 4 of whom had a sputum positive diagnosis and 2 patients fulfilled the Center for Disease Control (CDC) criteria for a presumptive diagnosis. Five patients clinically improved on empiric therapy for PCP but did not fulfill the criteria for the diagnosis of PCP according to CDC guidelines. The three remaining patients had clinical, radiographic, and/or histologic evidence of active alveolitis. In the abnormal group, the $T_{1/2}$ ranged from 2.0 to 25.5 min (mean = 4.8, s.d. = 5.7) for the ^{99m}Tc-DTPA and in the T-gas studies from 1.2 to 3.8 min (mean = 2.5, s.d. = 0.7). The clearance curves of all patients with abnormal studies were biexponential, enabling curve stripping of the slower late phase. As seen in Figure 1, the $T_{1/2}$ values in all these patients were clearly differentiated from those obtained in the normal individuals.

In the 22 nonsmoking patients who had normal lung clearance, there were 6 patients who were evaluated for the possibility of active alveolitis in whom other primary diagnoses were made. In this group, three patients had evidence of a connective tissue disorder, while two patients had evidence of airflow limitation on clinical and spirometric grounds. The remaining 16 patients were infected with the human immunodeficiency virus and of this group 13 had no clinical, radiographic or pathological evidence of active opportunistic lung infection. One patient had a postmortem diagnosis of miliary pulmonary tuberculosis while the remaining two patients had a presumptive diagnosis of PCP clinically but did not fulfill the CDC criteria

TABLE 1
Results: Lung Clearances (min)

	Normal	Smokers	Abnormals
No. of patients	22	14	14
DTPA			
Mean	52.5	28.3	4.8
s.d.	29.5	15.6	5.7
Range	19.8–132.4	10.0–42.0	2.0–25.5
T-Gas			
Mean	10.1	7.0	2.5
s.d.	2.4	1.1	0.7
Range	6.8–16.7	5.7–9.0	1.2–3.8

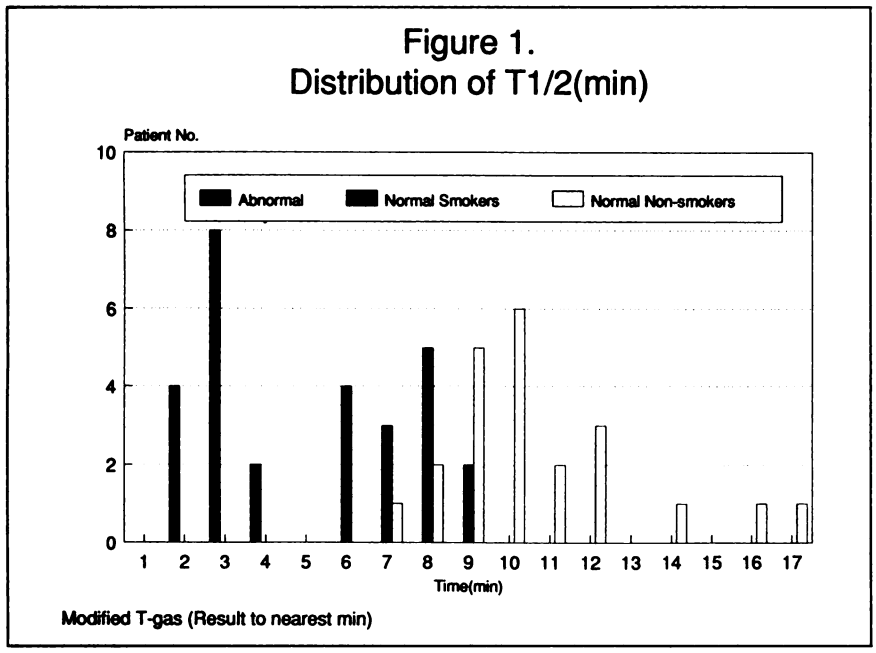

FIGURE 1. Distribution of lung clearance half-times using modified Technegas, showing clear separation of abnormal from nonsmoking normals and smokers.

for this diagnosis. The latter two patients clinically improved on empiric therapy for presumed PCP infection.

Eight patients had a second ^{99m}Tc-DTPA study 24 hr later to validate the results obtained by subtracting residual T-gas activity from the initial ^{99m}Tc-DTPA study. Six patients with no evidence of pulmonary pathology and normal initial ^{99m}Tc-DTPA lung clearances had a mean half-life of 55.1 min for the initial study and 53.2 min for the study obtained 24 hr later. There was no significant difference between the two mean values by the Students t Test ($p > 0.1$). Similarly, studies obtained in two patients with interstitial pneumonitis, provided an initial mean half-life of 6.7 min and 24 hr later a mean half-life of 6.9 min. The difference was not significant by the Students t Test ($p > 0.1$).

An aerosolized [^{99m}Tc]pertechnetate study was performed in four patients 24 hr later, for comparison with the earlier T-gas study, using the same equipment and procedure employed for the administration of DTPA aerosol and yielding the same size particles. The clearance values obtained for T-gas and [^{99m}Tc]pertechnetate are very similar (Table 2).

TABLE 2
Comparison of Lung Clearance of Different Ventilation Agents

	Half-life (min) in Four Patients		
Agent	DTPA	T-Gas	Pertechnetate
Normal	46.1	10.9	11.7
Normal	65.8	16.7	14.3
Smoker	42.3	5.7	6.6
PCP	3.5	3.4	3.3

DISCUSSION

The nature of Technegas, an ultra-fine dispersion of ^{99m}Tc-labeled carbon particles, clearly is critical in achieving peripheral penetration and distribution throughout the lungs, leading to ventilation images which have been shown to be diagnostically equal to, or even superior to ^{133}Xe (*8,9,10*) or to ^{81m}Kr (*11*). Much of this clinical utility, however, results from the feasibility of obtaining multiple views in a variety of projections. This is possible since, after inhalation into the lungs, a fraction of the particles lodge in the alveoli, but there is little or no washout from the lungs, the clearance rate declining with a half-life equal to that of ^{99m}Tc. However, as we have shown, the relatively minor modification of the method of generating the Technegas has a profound effect on the nature of the agent. Thus, in normal individuals, the mean half-clearance time from the lungs was 10.1 min. As expected, the values obtained in normal individuals who were smokers were faster, their mean half-clearance time being 7.0 min. This accelerated clearance in this group was also found in the same individuals when studied with ^{99m}Tc-DTPA aerosol.

It seems justifiable to postulate that the clearance being demonstrated using "modified" Technegas is that of pertechnetate. The reasons why Technegas should be modified by combustion in an altered atmosphere are still being investigated, as are the nature of the particles. However, the half-clearance times obtained in four patients with both modified Technegas and pertechnetate are remarkably similar and the whole-body distribution of radioactivity following pulmonary clearance of Technegas is that of the preferential uptake into those organs that specifically trap pertechnetate (Fig. 2). The half-clearance time values obtained with Technegas are of the same order as those

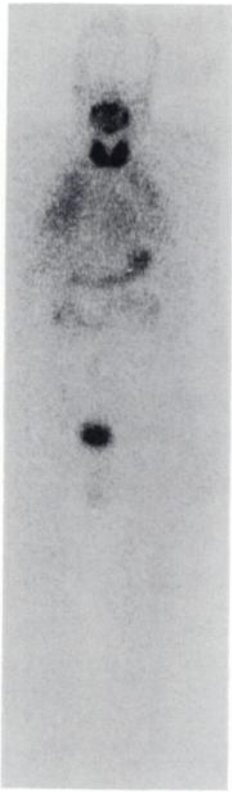

FIGURE 2. Whole-body scan showing distribution of radioactivity following pulmonary clearance of modified Technegas with preferential uptake in those organs that specifically trap pertechnetate.

that have been reported in the literature, for example by Chopra et al. (*1*). They and others (*2,12,13*) have shown with the use of radioaerosols that, in accord with Fick's laws of diffusion, the rate of diffusion of small molecules is inversely proportional to the square root of their molecular weights. In confirming that $^{99m}TcO_4$, with a molecular weight of 163, was cleared from the lungs more rapidly than ^{99m}Tc-DTPA (molecular weight 492) by an average factor of 3.3, Rinderknect et al. (*12*) actually favored the former for clinical use. They found that accelerated clearance could be identified in interstitial lung disease with both agents, but pertechnetate was more reliable in demonstrating the slow clearance associated with pulmonary alveolar proteinosis. Nevertheless, ^{99m}Tc-DTPA aerosol has subsequently been utilized in most studies of altered pulmonary clearance. This may in part have reflected concern regarding accurate quantitation of such a rapid clearance as occurs with pertechnetate with marked alterations of pulmonary permeability. There is no such problem with modern detection equipment and the availability of computers. It is also relevant to note that, because the clearance of pertechnetate is so rapid, the values will reflect only altered diffusion and should not be affected by changes in pulmonary blood flow. Such changes are, however, not encountered in the majority of patients in whom pulmonary clearance studies are now of routine clinical value, for example, those suspected of having opportunistic infections. Our results demonstrate that accurate differentiation of such patients from normal individuals, both smokers and nonsmokers, is achieved. Indeed, they were as readily identified by the nature of the computer-derived clearance curves as by the actual numerical value of the calculated half-clearance time.

The general use of ^{99m}Tc-DTPA for the measurement of pulmonary clearance has probably reflected the use of this radiopharmaceutical in radioaerosol ventilation undertaken routinely with lung perfusion in the investigation of suspected pulmonary embolism. Thus it is readily available for both purposes using the same apparatus. However, DTPA radioaerosol is not the ideal agent for such ventilation studies. In addition to superior peripheral penetration and decreased central deposition in comparison to DTPA radioaerosol, the administration of Technegas is simple and more rapid. These factors permit a marked improvement in counting statistics, therefore permitting images of high quality. These attributes of the technique are retained with "modified" Technegas. The ease of administration is certainly of importance, in view of the degree of illness usually encountered in the patients requiring investigation, whether, as in our series, those with interstitial pneumonitis, or those with acute lung injury in whom Barrowcliffe and Jones (*14*) found DTPA pulmonary clearance to be of value. Further confidence in the accuracy of the Technegas clearance value reflects the excellent counting statistics. This factor almost certainly ensured the identification of the markedly accelerated half-clearance time of 2.5 min in a patient in whom there was both radiological and pathological evidence of severe pulmonary fibrosis, but in whom, because of her difficulty in complying with the DTPA aerosol procedure and obtaining suboptimal counting statistics, the latter technique yielded a false-negative result with a normal value of 25.5 min. This reflected the difficulties inherent in the aerosol method when patients are severely dyspnoeic leading to an inability to inspire sufficient radioactivity to achieve optimal counting statistics.

Our experience does therefore indicate that, using this method to modify Technegas, it is possible to obtain accurate quantitation of the clearance from the lungs of the administered activity. This confident identification of the changes reflecting alterations in pulmonary epithelial permeability is of practical value since it can be obtained using the same equipment as is employed for routine radionuclide studies with standard Technegas, merely requiring the use of an alternative gas supply. The ^{99m}Tc-DTPA aerosol lung clearance studies contributed to patient management by enabling the early introduction of appropriate therapy, particularly in the HIV-infected patients in whom PCP infection is the most common cause for diffuse interstitial pneumonitis. The advantage of the lung clearance study is such that it provides a rapid answer regarding the possibility of interstitial pneumonitis and thus obviates the requirement for pulmonary radiogallium imaging. In view of the increasing realization of the diagnostic utility of lung clearance studies, both in adults and children (*5*), and the advantages of the standard Techne-

gas, we believe that this modified technique should find a major clinical application in the investigation of numerous pulmonary disorders.

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REFERENCES

1. Chopra SK, Taplin GV, Tashkin DP, Elam D. Lung clearance of soluble radioaerosols of different molecular weights in systemic sclerosis. *Thorax* 1979;34:63–67.
2. Coates G, O'Brodovich HM. Measurement of pulmonary epithelial permeability with ^{99m}Tc-DTPA aerosol. *Semin Nucl Med* 1986;16:275–284.
3. Mason GR, Duane GB, Mena I, Effros RM. Accelerated solute clearance in pneumocystis carinii pneumonia. *Am Rev Respir Dis* 1987;135:864–868.
4. O'Doherty MJ, Page CJ, Bradbeer CS, et al. The place of lung ^{99m}Tc-DTPA aerosol transfer in the investigation of lung infection in HIV positive patients. *Respir Med* 1989;83:395–401.
5. Van der Wall H, Murray IPC, Monaghan P, Mackey DWJ. Pulmonary radioaerosol clearance in interstitial pneumonitis. *Eur J Nucl Med* 1990;16:428.
6. Burch WM, Sullivan PJ, McLaren CJ. Technegas—a new ventilation agent for lung scanning. *Nuc Med Commun* 1986;7:865–871.
7. Hayes M. Taplin GV, Chopra SK, et al. Improved radioaerosol administration system for routine inhalation lung imaging. *Radiology* 1979;131:256–258.
8. Sullivan PJ, Burke WM, Burch WM, Lomas FE. A clinical comparison of technegas and xenon-133 in 50 patients with suspected pulmonary embolus. *Chest* 1988;94:300–304.
9. Fawdry R, Bush B, King T, Gruenewald S. Initial experience with technegas—a new ventilation agent. *J Nucl Med* 1988;29:765.
10. Rimkus DS, Ashburn WL. Lung ventilation scanning with a new carbon particle radioaerosol (technegas), preliminary patient studies. *Clin Nuc Med* 1990;4:222–226.
11. Hilson AJW, Pavia D, Diamond PD, Agnew JE. An ultrafine ^{99m}Tc aerosol (technegas) for lung ventilation scintigraphy—a comparison with Kr-81m. *J Nucl Med* 1989;30:744.
12. Rinderknecht J, Shapiro L, Krauthamer M, et al. Accelerated clearance of small solutes from the lungs in interstitial lung disease. *Am Rev Respir Dis* 1980;121:105–117.
13. Mason GR, Uszler JM, Effros RM, Reid E. Rapidly reversible alterations of pulmonary epithelial permeability induced by smoking. *Chest* 1983;1:6–11.
14. Barrowcliffe MP, Jones JG. Pulmonary clearance of ^{99m}Tc-DTPA in the diagnosis of evolution of increased permeability pulmonary oedema. *Anaes Intens Care* 1989;17:422–432.