Pulmonary technetium-99m diethylene triamine penta-acetic acid aerosol clearance as an index of lung injury

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Abstract. Although the clearance of an inhaled nebulised radioaerosol has long been employed as a measure of lung function, this test has not found favour in nuclear medicine units to the extent that might originally have been anticipated. In this review the theoretical basis of solute transfer is considered and the measurement of radioaerosol clearance discussed. Thereafter the various clinical applications of alveolar permeability measurement are outlined. Finally, possible reasons for the restricted clinical use of the diethylene triamine penta-acetic acid clearance technique are considered. It is concluded that the technique should provide a rapid screening evaluation of the HIV+ve patient presenting predominantly with chest symptoms.

Key words: Diethylene triamine penta-acetic acid – Aerosol – Lung injury – Alveolar epithelium

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Introduction

The clearance from the lung of an inhaled nebulised radioaerosol has been in use now for many years as a measure of lung function. The test has not only generated considerable physiological interest but has also been proposed as a sensitive and valuable means of detecting and quantifying a wide spectrum of subtle to clinically obvious degrees of lung injury. The test, however, has perhaps not been adopted by nuclear medicine units as much as its early promise seemed to justify. This review, after discussing the physiology of the test and its potential clinical applications, identifies some possible reasons for this.

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Theoretical basis of solute transfer

The pulmonary blood-gas barier

The barrier separating pulmonary capillary blood from alveolar air in a lung unit consists of vascular endothelium, alveolar epithelium and the intervening pulmonary interstitium. It also includes a film of fluid lining the airspace within which inhaled solutes are dissolved. Because they can penetrate cells directly, small lipophilic molecules, such as hexamethylpropylene amine oxime, rapidly penetrate the barrier [1] and the capacity for transfer from alveolus to blood is dependent on how rapidly they can be carried away from the barrier by pulmonary venous blood; i.e. their transfer rate is blood flow or perfusion-dependent. Transfer of hydrophilic solutes across the blood-gas barrier, on the other hand, is much slower as it depends on passive diffusion through the intercellular junctions of the epithelium and endothelium [2–4]; the cross-sectional area of these spaces is miniscule compared with the total surface area of the barrier. Blood flow exerts a negligible influence on the transfer rate of a hydrophilic solute, which is said, therefore, to be perfusion-independent, or alternatively diffusion-dependent. Nevertheless, as blood flow decreases to low levels, diffusion-dependent transfer gradually becomes perfusion-dependent.

Restricted and unrestricted diffusion

The diffusion rate of a hydrophilic solute in aqueous solution (free diffusion) is approximately inversely proportional to the cube root of molecular size. If a solute is small compared with the diameter of a pore in an epithelial or endothelial membrane through which it diffuses, then the transfer rate across the membrane is similar to the rate of free diffusion and can be described as unrestricted. If, on the other hand, the size of the molecule begins to approach that of the diameter of the pore, then diffusion is slowed to a rate less than the rate of free diffusion in solution, and diffusion across the membrane can be described as restricted. "Molecular sieving" is an apt term to describe this aspect of barrier function.

*Pulmonary alveolar epithelial permeability
as an index of lung damage*

Epithelial permeability is about 10 times lower than endothelial permeability. It is therefore the rate-limiting variable in the diffusion of solutes across the barrier [5] and can be quantified by measuring the rate of transfer of a hydrophilic solute from alveolus to blood. As the alveolar permeability to a hydrophilic solute is readily influenced by lung damage [6, 7], the rate of clearance of an inhaled nebulised solute has become established as a means of detecting and quantifying the severity of diffuse interstitial pulmonary disease [2, 3, 6–8]. Because of its availability and convenience, technetium-99m diethylene triamine penta-acetic acid (^{99m}Tc-DTPA) has become established as the solute for this approach. Following inhalation, ^{99m}Tc-DTPA is cleared from the distal airway into pulmonary capillary blood and ultimately excreted in the urine. The rate of disappearance can be monitored by continuous scintigraphic detection using a gamma camera or scintillation probe and expressed as a $t_{1/2}$ or rate constant of clearance.

Aerosol generation and delivery

The penetration into distal lung by an aerosol is dependent on nebulised particle size. Although the movement of gas in the airways beyond the 16th generation of bronchi is by molecular diffusion in air rather than convection [9], there is evidence that aerosol particles penetrate to the distal airways and alveoli. Thus, whilst the half-time of ^{99m}Tc-DTPA pulmonary clearance in normal dogs is about 20 min, it is increased by ligation of the pulmonary artery but not of the bronchial arteries [10]. Occlusion of both pulmonary and bronchial flows greatly increases the half-time because collateral bronchial flow is responsible for the clearance after pulmonary arterial occlusion.

Quantitative basis of epithelial transfer

In the lung, the transfer rate, J, of solute per unit of lung tissue can be defined in terms of the permeability-surface area (PS) product of the blood-gas barrier and the solute concentration, C, in alveolar fluid:

$$J = PS \cdot C. \tag{1}$$

Dividing both sides of the above equation by M, the amount of solute present, gives:

$$\frac{J}{M} = PS \cdot \frac{C}{M}.$$

J/M is the fractional clearance rate, k, of solute and C/M is equal to $1/V$, where V is alveolar fluid volume, so:

$$k = PS/V. \tag{2}$$

It can be seen from this that the rate constant of clearance is directly dependent on the permeability coefficient and surface area for exchange, and inversely dependent on the volume of alveolar fluid in which the solute is dispersed. The permeability coefficient itself can be expressed thus:

$$P = \frac{V \cdot k}{S}. \tag{3}$$

Factors determining clearance rate

The clearance rate of a solute from distal airway is dependent on several factors related to the properties of both the solute and the lung. As already mentioned, lipophilic solutes are cleared very rapidly as a result of their ability to cross the epithelium by direct cellular penetration. Since their removal rate is perfusion-dependent, they have no value for the determination of epithelial integrity in the setting of radiolabelled solute clearance studies. Hydrophilic solutes, in contrast, exchange across the alveolar epithelium much more slowly at rates which depend on molecular charge and size. At normal levels of pulmonary blood flow, their transfer rates are diffusion-dependent and unaffected by changes in blood flow. The pores in the alveolar epithelium through which hydrophilic solutes diffuse are electrically charged and this explains why the transfer rate of a solute is dependent to some extent on its charge as well as its size. This was demonstrated by Barrowcliffe et al. [11], who showed that neutral dextran has a shorter clearance half-time than similarly sized anionic or cationic dextran. The difference disappeared, however, following injury to the blood gas barrier induced by i.v. oleic acid, suggesting that the pore size and/or number increased and, additionally, lost charge.

The pulmonary factors of potential importance in determining the rate of solute transfer, apart from disease itself, include regional surface area available for exchange, regional lung volume, intra-alveolar pressure, the composition and volume of the fluid in the alveoli, surfactant, and back-diffusion of solute from blood to lung interstitium.

Surface area, lung volume and intra-alveolar pressure are closely related in their effects on solute clearance rate. Marks et al. [12] addressed surface area and lung volume by measuring half-time of ^{99m}Tc-DTPA clearance at resting and elevated lung volumes. They were unable to distinguish between lung volume itself and the increase in surface area that accompanies an increase in lung volume, whether it was during or after inhalation of the solute. Expansion of the lung might be expected to stretch epithelial cells and pull them apart, thereby enlarging the diameter of the pores. Because of the arrangement of the alveolar septa in pleats, however, expansion in lung volume may not necessarily be associated with stretching of the alveolar walls [12, 13].

Surfactant seems to play a role in determining epithelial permeability to hydrophilic solutes but the mechanism is unclear [14]. Alveolar fluid volume and diffusion distances within the alveolus are difficult to study.

Although it is evident from Eq. 2 that an increase in fluid volume would, by itself, be expected to decrease solute transfer rate as a result of a lower intra-alveolar fluid solute concentration, cardiogenic pulmonary oedema is not associated with reduced solute clearance [15]. Pulmonay oedema due to lung injury, on the other hand, results in a greatly increased transfer rate by virtue of an increase in permeability.

The bi-exponential clearance

An interesting feature of the severely injured lung is that the clearance curve may become bi-exponential [16]. It has been suggested that this is the result of two populations of lung units with different degrees of damage and correspondingly different clearance rates. The evidence for this is that lung damage produced by i.v. oleic acid is not homogeneous. However, a biexponential curve is often seen when the clearance rate is markedly increased from any cause, raising the possibility of other explanations for the bi-exponential shape. These include firstly, deposition of aerosol more proximally in the airway, with slower clearance, and secondly, back-diffusion of tracer from blood to interstitium. It is easy to see how the latter could contribute towards a slower exponential, especially if alveolar fluid volume was increased as a direct consequence of an increase in permeability.

Effects of cigarette smoking

Cigarette smokers with normal lung function have an increased clearance rate [3, 17, 18] which effectively disqualifies them from the test. An approach which might be applicable to smokers is the simultaneous use of two tracers [19, 20]. By inhaling two solutes of different size and measuring k for both, V/S in Eq. 2 cancels out because it is identical for the two solutes and

$$k_1/k_2 = P_1/P_2. \tag{4}$$

If P_1/P_2 is greater than the ratio of free diffusion coefficients of the two solutes then restricted diffusion to at least the larger of the two must be present [21–23]. If smoking failed to influence restriction to diffusion, k_1/k_2 would be unaffected and consequently transparent to the possible effects of disease.

Restriction to diffusion is closely related to the radius of the solute in relation to the radius of the pore; if pore radius were to increase, then restriction to diffusion of a given solute may be lost. If the increased clearance rate of a solute in smokers is not the result of an increase in pore radius then restriction to diffusion of a critical sized solute may be retained. Based on pore theory, the rate constant of clearance of solute across the epithelium can be described by:

$$k = D \cdot \frac{A/\Delta x}{V} \cdot F, \tag{5}$$

where D is the free diffusion coefficient, A is the total cross-sectional area of pores and Δx is path length. F is a constant which is a function of the ratio of the molecular radius (a) of the solute to pore radius (r); it ranges from 0 for a completely non-permeable solute to 1 for a freely diffusing solute (i.e. no restriction) and incorporates the effect of electrical charge [21, 22]. Smoking could increase clearance by increasing A (i.e. increasing pore number), increasing r, changing the electrical charge of the pores, or decreasing alveolar fluid volume. A failure of smoking to induce any change in the ratio of clearances would argue against the predominant effect being on F, and therefore on pore radius.

Measurement of radioaerosol clearance

^{99m}Tc-DTPA aerosol can be nebulised and delivered using conventional systems designed for routine ventilation imaging as apart of a V/Q scan. Immediately following the inhalation of aerosol, the count rate over the lung is continuously monitored with a scintillation probe or a gamma camera. Scintillation probes are more suited to the ICU, but a gamma camera is preferable if logistically possible. The curve recorded during the first 7–10 min in a normal subject is generally a straight line on a semilogarithmic plot but it then "flattens off", partly because of recirculating intravascular tracer. When using a probe, the estimation of this blood background activity has conventionally been based on the count rate recorded from the thigh with a separate scintillation probe. The relationship between the thigh count rate and the pulmonary background signal is determined by giving an i.v. injection of a small dose of ^{99m}Tc-DTPA after the aerosol clearance rate has been measured. This approach assumes that the distribution of solute between intravascular and extravascular spaces is the same in the two regions. Since after i.v. ^{99m}Tc-DTPA, the pulmonay signal is predominantly an intravascular one, while the thigh signal is an extravascular one, this assumption is erroneous for the thigh. Use of a gamma camera to monitor pulmonary activity widens the scope of background correction since regions of interest can be placed over extrapulmonary tissues other than a limb. A useful background tissue is the liver since its extracellular space consists of intravascular and extravascular spaces of similar relative volumes as in the lung [24]. It is, furthermore, included in the field of view of the camera and projects a reasonably large area over which to place a region of interest. Conventionally, the i.v. dose of ^{99m}Tc-DTPA for calibration of background is given after the inhalation dose, but it is preferable to give it before because, as a smaller signal, it is more accurate to subtract it from the succeeding larger inhalation signal than the other way round. Indeed, it is not necessary to subtract the i.v. signal from the subsequent inhalation signal because since the liver curve has a shape identical to the intravascular background curve in the lung [24] it can be used for background subtraction at

any stage of the lung curve, before or after inhalation. Indeed, it can be imagined that the i.v. dose has essentially the same effect as an early rapid transfer of ^{99m}Tc-DTPA from alveolus to blood.

Irrational approaches to background correction may be the main reason why several authorities have concluded that background subtraction causes more error than it corrects. In any event background correction is probably unnecessary for routine measurements, provided the rate constant is based on no more than the first 10 min of data recorded after inhalation. In normal individuals, the clearance rate of ^{99m}Tc-DTPA is about 0.01 min^{-1}, or 1% per min. It is, however, about 4% per min in normal cigarette smokers.

Clinical applications
of alveolar permeability measurement

Although measurements of pulmonary epithelial permeability are simple to perform and allow insight into several pathological processes in the lung, they have made little clinical impact. Why is this? Before considering this question, it is necessary to briefly review the disease processes where the technique may make a useful clinical contribution. Although varied, these are largely confined to diseases which would be expected to cause an abnormality of the lung parenchyma. A knowledge of the physiological processes that result in changes of permeability, defined by either the half-time of clearance or a modified rate, is essential and outlined above.

Diseases causing pulmonary epithelial abnormalities are numerous. Pulmonary inflammatory diseases may be due to a variety of allergens or infective agents or may be iatrogenic. Pointers to the disease process may be obtained from the clinical history, for example the patient's occupation, hobbies and medication, or from a history of immunosuppression related to the immunodeficiency virus (HIV) or drug therapy. Progressive deterioration in lung function may initially occur in the presence of a normal chest radiograph or more commonly with one showing infiltrates.

Alveolitis

Extrinsic allergic alveolitis and cryptogenic fibrosing alveolitis may lead to oedema, and thickening and disruption of the alveolar walls and basement membrane. In pigeon fancier's lung, ^{99m}Tc-DTPA transfer is abnormal [25], and shows an increased clearance rate which is proportional to circulating antibody titre. Patients without circulating antibody but with a history of antigen exposure have clearance times faster than normal controls but not as fast as those with detectable antibody. Pulmonary function tests are often normal in the presence of accelerated clearance rates. Similarly, cryptogenic fibrosing alveolitis or alveolitis associated with connective

tissue diseases [26] is associated with an increase in the transfer rate of ^{99m}Tc-DTPA. In cryptogenic fibrosing alveolitis, serial measurements of ^{99m}Tc-DTPA clearance have been used to monitor therapeutic response [27, 28]. Labrune et al. [27] demonstrated that the clearance rate decreased following a positive clinical response to corticosteroids but not down to normal levels. This persistent increase in the clearance rate may be the result of irreversible stretching of lung units by fibrosis. Uh et al. [29] found that in patients with diffuse infiltrative lung disease, clearance rates were significantly faster in all lobes compared with normal controls but that, compared with late disease, early stage disease was associated with slower clearance in the upper and middle lobes. There was, however, overlap between the ranges in normals and those with disease such that it was difficult to use the test to identify patients with disease but with normal carbon monoxide transfer values. Thus, although the clearance rate is unlikely to be a diagnostic test, it may be used to monitor therapy and relapse.

Connective tissue disorders affecting the lung

Most connective tissue diseases can potentially affect the lung. The inflammatory process usually affects the bases more than the apices. Chopra et al. [2] studied a group of patients with systemic sclerosis and found that the DTPA clearance was much faster in the affected lower zones. Similarly increased clearance rates would be anticipated in association with the acute changes of rheumatoid arthritis and polyarthritis nodosa.

Sarcoidosis

Sarcoidosis is a multi-system inflammatory granulomatosis disease which preominantly presents with pulmonary involvement but can affect almost any organ. Presenting features in relation to the lung are pulmonary infiltrates and/or hilar or mediastinal lymphadenopathy. The chest radiograph however, is, highly insensitive and up to 60% of patients with parenchymal granulomata may have a normal chest radiograph. An increase in pulmonary alveolar permeability has been observed in all grades of pulmonary sarcoidosis [30–32]. The DTPA transfer rate increases with deterioration in pulmonary function and decreases in response to treatment with corticosteroids [30]. Clearance rates appear to be related to the degree of inflammation but have no definite relationship to serum angiotensin converting enzyme levels or the lymphocyte content of bronchoalveolar lavage fluid.

Drug- and radiation-induced pneumonitis

Several drugs, including bleomycin and amiodarone, can cause a pneumonitis. A clinical difficulty with such drug

toxicity is in the distinction of alveolitis from interstitial pulmonary oedema due to heart failure, since the drug may be used in patients with cardiac disease or alternatively cardiac disease may be associated with therapy. Cardiac failure does not significantly alter alveolar capillary permeability and so the clearance rate of DTPA in these conditions is normal [15] and should be able to separate cardiogenic from an alveolitic cause of breathlessness. Terra-Filho et al. [33] demonstrated that clearance rates were faster than in normal smokers and in patients receiving amiodarone but with no respiratory problems. DTPA clearance was more sensitive than spirometry in the detection of this condition. The test would not have been able, however, to identify pneumonitis in smokers. Further abnormalities have been reported in the inflammatory response associated with "crack" use, in which increased clearance rates have been reported [34].

Adult respiratory distress syndrome

Pulmonary alveolar DTPA transfer is accelerated in adult respiratory distress syndrome (ARDS) [4, 5, 15, 35, 36], in which the severity of endothelial damage has also been quantified with indium-113m transferrin accumulation within the lung interstitial space. Braude et al. [5, 36] found a correlation between alveolar permeability to DTPA and endothelial permeability to transferrin in patients with ARDS, illustrating that the diffusion of molecules from the vasculature to the interstitium can give results comparable with diffusion from airspace to vasculature.

Detection of inflammation/infection in the lungs of immunosuppressed patients

The lung is often damaged by infection or inflammation in the immunocompromised host, with a resulting high mortality. There are many potential causes of fever in this group, which tends to prompt empirical therapy. Patients are often debilitated from their underlying disease and so invasive investigations are hazardous. The frequency of certain infections varies between HIV+ve patients and those with other causes of immunosuppression; for example, transplanted patients have a higher incidence of cytomegalovirus (CMV) infection [37], whilst HIV+ve patients have a higher incidence of Pneumocystis carinii pneumonia (PCP) and bacterial infections such as Streptococcus pneumoniae, Pseudomonas aeruginosa and mycobacteria. Fungal infections may occur in either group.

In the patient who is neutropenic as a result of chemotherapy, the investigating clinician needs an instant test to demonstrate the type and distribution of abnormality in order to direct further investigation. DTPA clearance can demonstrate the location of the main ven-

tilatory abnormality before changes in the chest radiograph if there is a focal problem such as lobar pneumonia, segmental infection or pneumonitis. Thus in renal transplant recipients, PCP is associated with a rapid transfer rate of DTPA [38]. These changes, however, would also occur with CMV infection, which is common in transplant recipients, whereas fluid overload or a bacteriopneumonia would not cause significant abnormalities. The clinician can be directed towards a definitive invasive test, such as transbronchial biopsy, or an urgent induced-sputum examination.

Pulmonary DTPA transfer rate can give rapid clear guidance as to whether there is pulmonary pathology in patients with HIV infection who have cough, breathlessness and fever, and often the likely nature of that pathology. The technique has been used in PCP and other lung infections by a number of groups [39–45], all of whom have documented a rapid clearance rate. Studies have shown that in alveolitis, the clearance curve is biphasic with a rapid first component (half-time less than 4 min; 12.5% per min). The most likely cause of an alveolitis with this biphasic pattern in HIV-ve patients is still PCP but other causes include CMV infection, lymphocytic interstitial pneumonitis and non-specific interstitial pneumonitis. The test has a high sensitivity and specificity for PCP in this patient population but false-negative results may occur [42]. Occasionally a biphasic curve is found in heavy smokers with HIV infection in the absence of an alveolitis and it is therefore suggested that baseline scans are obtained in all smokers (authors' experience). Transfer times are generally not biexponential in other bacterial infections with the exception of Legionella pneumophila [41]. Rosso et al. [40] have demonstrated that the DTPA technique has a higher sensitivity than gallium-67 scanning (92% compared with the 72%) for infectious pulmonary complications. This difference is more marked for patients with normal chest radiographs and normal blood gases. The combination of a normal chest radiograph and a normal DTPA clearance virtually excludes pulmonary infection/inflammation significant enough to require therapy. A recent review of DTPA transfer in HIV+ve patients has outlined an algorithm for its use in HIV infection [45]; this will continue to be of use only while PCP is the most common cause of alveolitis in HIV+ve patients.

Heart/lung transplants

DTPA clearance has been used to identify rejection in patients with lung transplants [46–48]. The clearance was faster in patients with lung transplants (2.62%±0.25%/min) than in non-smoking controls (1.2%±0.12% /min) but increased further during rejection (3.65%±0.41%), giving a sensitivity and specificity of 69% and 82% respectively. These data suggest that the technique may be a simple method for monitoring this patient group, indicating biopsy if the clearance is increasing. Other pathologies such as

CMV and PCP would be expected to result in similar changes in clearance.

Why is the DTPA clearance technique not in wider clinical use?

As with many other nuclear medicine investigations, the technique, although non-specific, is rapid, easy to perform and extremely sensitive in the detection of lung pathology in certain circumstances. It has been applied only to HIV+ve patients in any sizeable numbers and more recently to patients with fibrosing alveolitis. The strength of the test is its ease of use and sensitivity in the detection of a pulmonary abnormality. Its major weakness is that smokers also have an abnormally fast clearance half time, although, as mentioned above, this might be circumvented by dual isotope studies. The test is reproducible and so capable of following individual patients before and after therapy.

Patients in whom the test should be at an advantage are those who are HIV+ve with a cough and/or fever. The technique should be available on a same-day basis, thereby leading to a real improvement in patient management. The utility is particularly high in patients with a normal chest radiograph in whom urgent further investigations may be directed. As an alternative, gallium-67 imaging takes several days to organize and complete and is more expensive than a clearance study. Nevertheless, it may give additional useful information on the presence or otherwise of disease elsewhere in the body, particularly lymph node disease. If available on the same day or within 24 h, a clearance measurement may be useful for patient reassurance if normal or to suggest urgent investigation or empirical therapy if abnormal.

There are a number of explanations for the unpopularity of the technique:

1. *Other centres have tried the test and found it to be unhelpful.* There is no evidence in the literature to support this contention.
2. *The technique is cheaper than gallium imaging, with less revenue to the department and individuals performing the test.* This is unlikely in the current financial climate.
3. *The clinician prefers to have definite histological proof and therefore opt for an induced sputum examination or bronchoscopy.* The failure rate of induced sputum examination is high, especially in the presence of a normal or near-normal chest radiograph. Bronchoscopy is expensive, invasive and carries a definite risk. It is too expensive to carry out in all patients with a cough and fever, in whom there is a suspicion of PCP. The DTPA technique should allow patient selection but the additional cost may not be favoured by the clinician who is capable of performing the bronchoscopy on his/her own patients.
4. *Poor education of clinical colleagues by the nuclear medicine physicians.* This may be true.
5. *Patients with HIV are concentrated in major cities in Europe, the United States and Australia and thus limited numbers of hospitals see large numbers of such patients.* Policies will be forged by previous experience and so changing from a technique such as gallium scanning, with which clinicians have become accustomed during the emergence of AIDS in the United States, will be difficult, in spite of the demonstration by Rosso et al. [40] of a higher sensitivity for the detection of lung pathology.
6. *The technique is limited to the identification of problems in the lung parenchyma, particularly alveolitis.* Certainly, gallium has the advantage that it may demonstrate other pathology in the lung and in lymph nodes.
7. *Since the technique has to be made available every day at short notice, it is not compatible with the routine practice of nuclear medicine departments.* Busy departments, where the test is likely to be offered, usually make provision for urgent investigations.
8. *Clinicians, nurses and technicians are still inherently concerned about the potential infection hazard of HIV+ve patients and will be resistant to a scanning service in this patient group.* Further reassurance may be necessary.

The DTPA clearance technique should provide a rapid screening evaluation of the HIV+ve patient with predominantly chest symptoms. Gallium scanning should be reserved for patients with pyrexia of unknown origin. Neither test will be utilized by the clinician who believes bronchoscopy should be used as the first investigation after the chest radiograph in all patients with chest symptoms.

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