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Clinical Application of Radioaerosol Studies — pulmonary embolism, inhalation burns and glue-sniffers and COPD

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Introduction

The alveolar epithelium and the capillary endothelium together form the alveolar capillary membrane. Fluid exchange occurs across this membrane, and is dependent on intravascular and interstitial hydrostatic and oncotic pressures, and on permeability of this membrane. Damage to either the avleolar or capillary component can result in a high permeability pulmonary oedema, even though the alveolar epithelium forms an extremely tight membrane which is ten times less permeable than the capillary endothelium [1].

Nuclear medicine methods can be used to observe changes in integrity of pulmonary capillary endothelium (with first pass dual-indicator dilution technique using successive injections of radiotracer [2]), and of alveolar epithelium, and it is important that the damage should be detected before patients develop clinical pulmonary oedema, so that intensive therapy can be instituted early. We have used ^{99m}Tc DTPA radioaerosol to measure alteration in pulmonary epithelial permeability and to image the distribution of ventilation in normal and some pathologicl states. In some clinical studies Tc-99m (tin) colloid radioaerosol has been used to obtain the ventilation images.

Methods

Ventilation studies with radioaeorols for pulmonary embolism have been done routinely in Nuclear Medicine Department, Singapore General Hospital since 1986. Most of the patients who had a high clinical suspicion e.g. calf pain and swelling had bipedal radionuclide venograms done using ^{99m}Tc colloid or the lung perfusion agent, ^{99m}Tc MAA. The ventilation scan is generally done first followed by the perfusion scan. The high count-rate from ^{99m}Tc MAA permits adequate images without significant shine-through from the radioaerosol ventilation study. Clearance measurements of ^{99m}Tc DTPA aerosol across the alveolar capillary membrane were done initially in 12 normal volunteers (army personnel) and in 8 patients with low susplcion of inhalation burns i.e. exposure to fire only at limb extremeties. Subsequently in 1987, all patients with burns who were entered into a study protocol for burns also had the radioaerosol clearance study, and to date 48 patients with suspicion of inhalation burns have been studied.

In the same period we studied 10 cigarette smokers to confirm the rapid radioaerosol clearance from the lungs in this group. 20 young hardcore glue sniffers from the Sembawang Detention Centre were studied to note any alveolar-capillary membrane damage from inhalant abuse. Most of these young men were smokers, and since smoking and glue-sniffing was forbidden at the Centre, we were also able to study the effects of cessation for varying periods on the clearance rate of the radioaerosol from the lungs in glue-sniffing. In 1988 we particlpated in a programme with the International Atomic Energy Agency (IAEA) to image the ventilation of the lung in chronic obstructive pulmonary disease (COPD) with ^{99m}Tc tin colloid aerosol, and to compare this with perfusion of the lung using ^{99m}Tc macroaggregated albumin (MAA). We took this opportunity to study also the lung clearance of ^{99m}Tc DTPA radioaerosol in 8 of these patients. In these COPD patients we noted the deposition pattern of inhaled radiocolloid aerosol to help differentiate the nature of the obstructive airways disease. Chest X-ray was done routinely and all of them had lung function tests done, with only those patients having a FEV 1 of $< 70\%$ being entered into the study.

The subjects breathe a submicronic aerosol of ^{99m}Tc DTPA (1 um mean mass aerodynamic diameter, CADEMA, USA, or BARC Generator, India) for 2-3 min after instillation of 20-25 mCi (740-925 MBq) of freshly prepared ^{99m}Tc DTPA into the nebuliser. The radioactive solute was prepared by adding the technetium-99m dose in 2 ml physiological saline into a commercial vial of DTPA (Amersham UK), and the binding of ^{99m}Tc to DTPA was about 95% using paper chromatography. The nebuliser was connected to the wall oxygen supply and a flow rate of 10 L/min was used. Immediately following the radioaerosol inhalation in a lying position, a dynamic acquisition was started using an Elscint Apex 409A gamma camera/computer system with the patient supine and the gamma-cameral placed posteriorly over the lungs. 20 frames at 1 minute per frame were acquired over the 20 minute period using a 64×64 spatial resolution. Subsequent reframing was done to produce a single reframed image and regions of interest (ROI'S) were drawn around each lung or parts of the lung. Time-activity curves were then obtained for each region/lung and an exponential fit was performed on the time-activity curves to obtain a clearance half-time ($T^{1}/_{2}$) i.e. time for 50% of the radioaerosol to clear from the lung. Retention images were also generated to note any discrepancy in reglonal lung clearance of ^{99m}Tc DTPA aerosol. No corrections were made for contribution of circulating and tissue radioactivity to the total counts detected over the lung field i.e. non-lung parenchymal radioactivity, as this is usually minimal.

The ventilation study was generally done within 3 days of admission in the burns patients. Serial studies were done in some patients in hospital and as outpatients.

Fibreoptic bronchoscopy was usually done within a day of the burns, using on Olympus bronchofibrescope BF Type B2. The severity of damage noted at bron-

choscopy was graded as follows:
0=normal
1=mild oedema and hyperemia
2=moderate oedema, hyperemia and secretions
3=severe oedema, inflammation, ulceration and slough

Twelve of the burns patients studied were Koreans who were involved in an ammonia tank explosion on board a ship. The remaining 36 were patients from Singapore who were exposed accidentally to kerosine stove fires or gas explosions, or who had attempted suicide.

Results

1. Pulmonary Embolism

An average of 250 ventilation/perfusion lung scans are done per year in the department for pulmonary embolism. Approximately 100 radionuclide venograms are done. The incidence of V/Q mismatch is about 40% and using Biello's criteria [4], about 15% were high probability scans for pulmonary embolism. We have not done any comparative studies between V/Q scanning and pulmonary angiography, or between radionuclide and contrast venograms. An example of V/Q mismatch is shown in Figure 1.

Table 1. Summary of Bronchoscopy and Ventilation Study Results (Burns Patients)

Total number of patients = 65
No of poatients with bronchoscopy and ventilation study = 42
Normal subjects: $T^1/2$ = 66±lSD of 12 min
(No = 20)
Burns Patients: $T^1/2$ = 35±lSD of 12 min
(No = 42)

Bronchoscopy	Grade 0+1	Grade 2	Grade 3	Total No
Normal $T^1/2$ (mean = 60 mins)	No = 16	4	4	24
Abnormal $T^1/2$ (mean = 31 mins)	No = 4	2	12	18
Total No	20	6	16	42

2. Inhalation Burns

Table 1 summarises the findings in the study of normals and in patients with suspected inhalation burns, while Table 2 notes the change in clearance rates over a period of time in three patients with inhalation burns. Figure 2 and Figure 3 show the time-activity clearance curves and the retention images in a normal and abnormal study respectively.

In the 12 normal, non-smoking adult volunteers and in the 8 patients with a low suspicion of inhalation injury, the $T^{1/2}$ ranged from 47 to 78 min with a mean of 66 min$\pm$1SD of 12 min. The volunteers were in their twenties while the patients were in the 30-45 age group. There were no significant differences in clearance between right and left lungs.

In the group of 65 patients with suspicion of inhalation injury, only 42 had both bronchoscopy and ventilation study; of these 42, 12 were Korean males in their thirties. They were exposed to ammonia from an ammonia thank explosion on board a ship in the South China Sea and they were flown to the Singapore General Hospital the same day and managed by the burns Unit in this hospital. An inhalation injury caused by chemicals was presumed and though 15 were transferred from the ship to hospital only 12 were able to have the aerosol studies done. All these twelve also had bronchoscopy done mostly within a day after admission, though in one of them the delay was 5 days. There were 30 local patients, who had both bronchoscopy and ventilation study done. This group of patients was exposed to thermal injury or products of combustion.

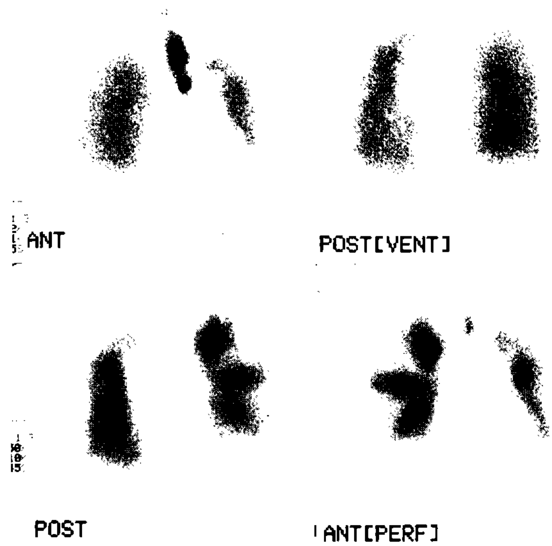


Fig. 1

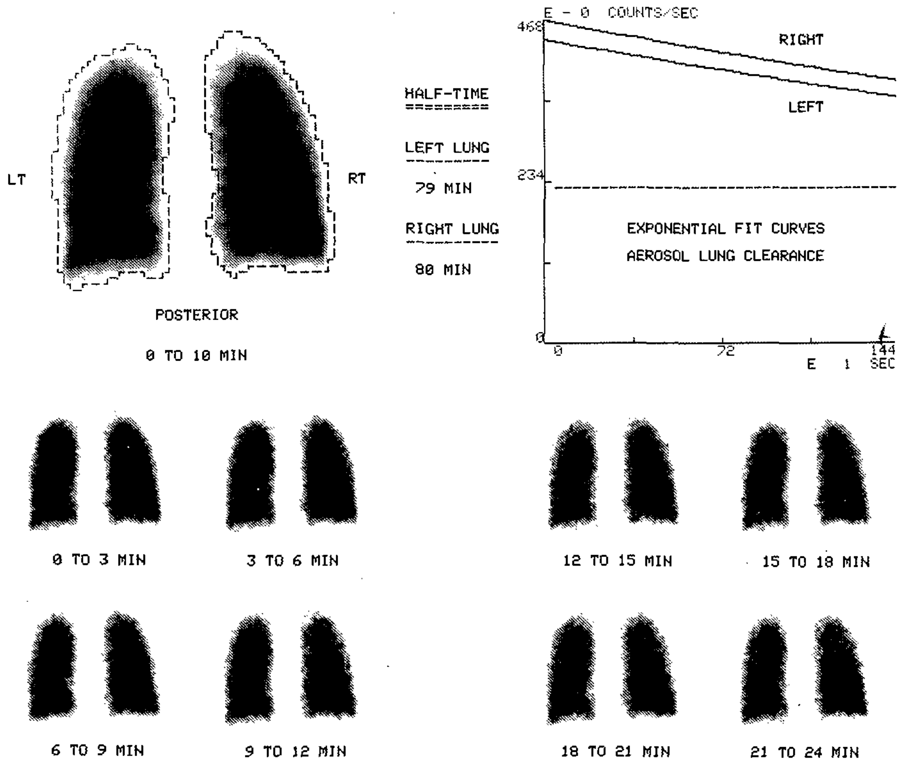
Table 2. Change in clearance rates with time (Burns Patients)

Name	Date	Right Lung $T^{1/2}$	Left Lung $T^{1/2}$	Chest X-ray
BJU	16.12.87	29 min	24 min	Normal.
	31.12.87	33 min	25 min	Patchy bilateral opacities.
	20.01.88	35 min	35 min	Patchy bilateral opacities.
KMS	15.12.87	25 min	31 min	Increased markings right lower zone.
	2.01.88	18 min	18 min	Increased markings right lower zone.
	4.01.88	23 min	24 min	Right lower zone effusion and patchy left lower zone.
JUB	16.12.87	40 min	34 min	Normal.
	30.12.87	70 min	50 min	Normal.

Table 3. COPD Ventilation Perfusion Study

Clinical Diagnosis	No of Patients	Aerosol Deposition Pattern	Perfusion Scan AN	Perfusion Scan N	Chest X-ray
Emphysema (E)	9	Central (C)	9	0	HIL
Bronchitis (B)	7	Peripheral (P)	5	2	ILM
Mixed	8	C+P	8	0	both

AN = Abnormal HIL = hyperinflated lung
N = Normal ILM = increased lung markings
Clearance $T^{1/2}$ in 18 patients (9E, 9B) = $78 \pm 1SD$ 14 min.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0
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144
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12 TO 15 MIN
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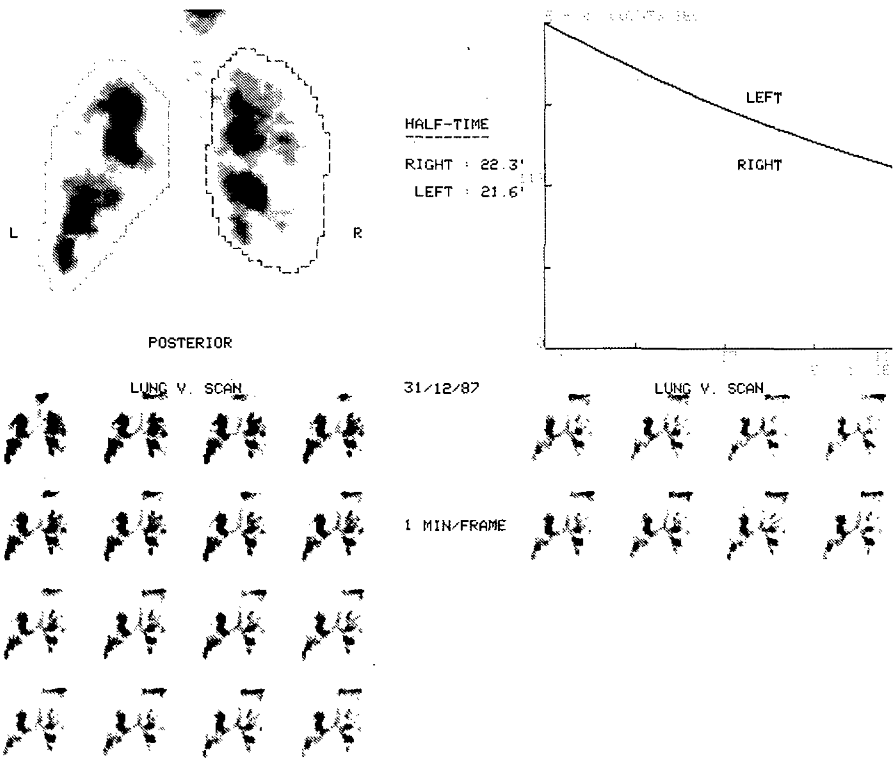
9 TO 12 MIN
18 TO 21 MIN
21 TO 24 MIN

Fig. 2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1 MIN/FRAME

Fig. 3

The retention images in normal subjects showed more clearance of tracer in the apices and edges of the lung fields at the end of the study period. Similarly in the patients with abnormal bronchoscopic findings the ventilation images generally showed patchy radioaerosol distribution in both lungs, while the retention images showed obvious increased regional clearance in only a few patients with high likelihood of lung parenchymal damage. Chest X-rays were normal in most of the patients at time of ventilation study, though subsequent films did show evidence of bilateral patchy infiltration (pneumonitis) or oedema, particularly in the basal areas. Pulmonary function measurement was done in only a few patients and no analysis could be done. There was no correlation between the partial pressure of arterial oxygen PaO_2, and the grading of bronchoscoplc findings or the ventilation study $T^1/_2$ results.

3. Chronic Obstructive Pulmonary Disease (COPD)

Table 3 summarises the results of aerosol deposition pattern and clearance times in patients with COPD. It is to be noted that the radioaerosol deposition tends to be central in patients with emphysema, and more peripheral in bronchitic patients, while a fair number of patients will tend to show a mixed pattern. The chest X ray can be normal in some of these patients. The mean $T^1/_2$ from ^{99m}Tc DTPA clearance in these patients was 78 min. The perfusion images largely matched the ventilation images in these patients with COPD.

Figures 4 and 5 show patterns of aerosol deposition in moderate and severe COPD together with clearance curves.

4. Smokers and Glue-Sniffers

In this group, there were 10 smokers (Volunteers) and 20 glue-sniffers from Sembawang Detention Centre. The smokers had an abnormally rapid mean $T^1/_2$ clearance time of 20 min; as can be seen from Figure 6, in the glue sniffers, the longer the period of abstinence from cigarettes, the larger the $T^1/_2$ clearance times obtained. In only 1 of the gluesniffers who was always a non-smoker, and stopped glue sniffing for 30 days, was the $T^1/_2$ abnormal i.e. 36 min, indicating that there is some alveolar-capillary damage in long-term hard-core glue-sniffers. It also appears that the recovery of clearance times to normal on cessation of smoking is prolonged in the glue-sniffers, apart from neurological damage.

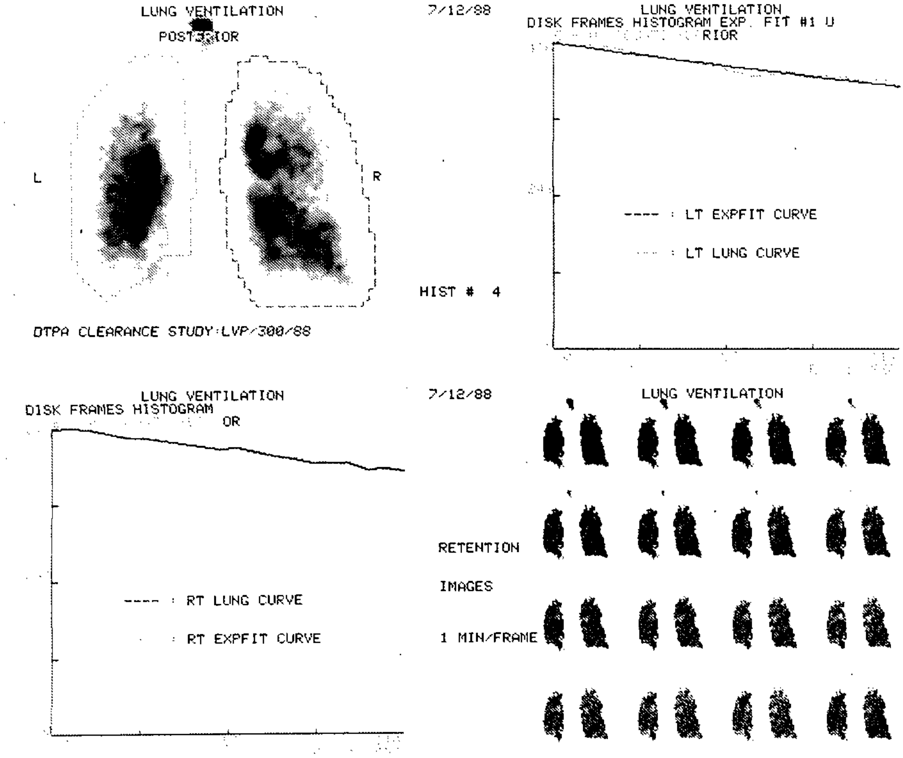
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Fig. 4

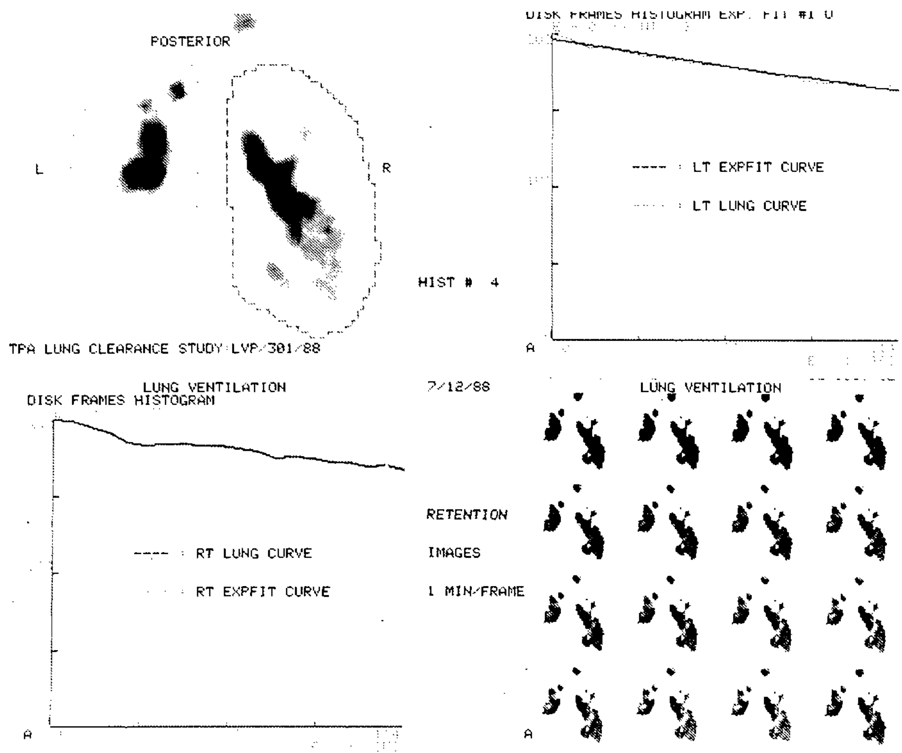
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Fig. 5

Discussion

Normals

Our group of 12 normal volunteers and 8 patients with burns at limb extremeties was fairly young i.e. mean age=26. The mean clearance T½ obtained was 66 min, and this is slightly lower than that reported from other centres, where older volunteers were studied. A previous study [3] has shown a variation in clearnance T½ with age, with younger volunteers showing a more rapid clearance; this accounts for our slightly lower normal values.

Pulmonary Embolism

Pulmonary embolism is probably underdiagnosed in our Asian countries partly due to varied presentation and partly due to inadequate equipment for ventilation lung scanning, particularly the lack of cheap radioaerosol delivery systems. This has been overcome with the BARC Generator from Bombay, India. There is also a general belief that DVT and PE occur infrequently in our Asian populations.

Though we generally do the ventilation scan first, it is possible to use low dose ^{99m}Tc MAA for perfusion scanning, and to proceed with the ventilation study only if the perfusion scan is abnormal. This could be done especially in patients in whom the chest X-ray is normal with the patient having a low clinical suspicion of pulmonary embolism [5]. It has been shown that normal and high-probability lung scans correlate well with pulmonary angiography, while the low probability lung scan is a good marker of those patients at a very low risk of recurrent thromboembolic events when left untreated [6].

Surface contamination in rooms where radioaerosol studies are done may be significant and hence due care must be taken to ensure proper technique and to monitor equipment and persoinnel with wipe tests [7]. This would not appear to be a significant problem with the BARC Generator. We have no experience with Technegas.

Smokers and glue-sniffers

Cigarette smoking is known to cause increased ^{99m}Tc DTPA pulmonary clearance [8,9], and this has been borne out in our study of 10 smokers where the mean T½ is considerably reduced to 20 min. Studies on regular smokers who stopped smoking have shown that the increased clearance rate returned towards normal, with a significant improvement (decreased rate) in T½ as early as 24 hr [10]. However in our study of young hard-core glue-sniffers this does not appear to be so. We have studied the pulmonary clearance in these 20 young men from the Sembawang Detention Centre, where they were off cigarettes and glue-sniffing for periods ranging from 1 day to 30 days. Unfortunately, owing to transport and detention logistics, there are not many in each group of days off smoking, but it appears that even up to one week, the clearance-rates are faster than normal. As can be seen from Figure 6 even at four weeks, the clearance-rates are just about approaching the normal range. This indicates that with the superimposition of inhalant abuse on smoking, there is prolonged alteration of the alveolar capillary membrane permeability. Only one out of the 20 men was a regular non-smoker whom we studied at day 30, and he had an abnormal T½ of 36 min, suggesting altered alveolar-capillary permeability from inhalant abuse alone. The information in Figure 6 can be utilised in anti-smoking clinics and in rehabilitation of glue-sniffers.

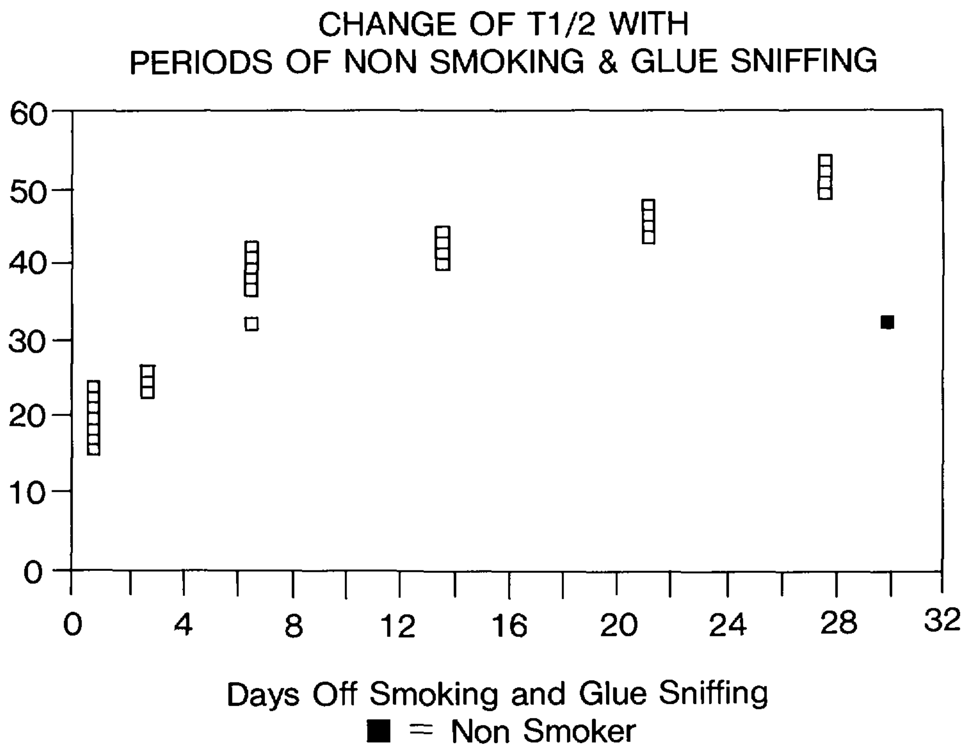

Fig. 6

Inhalation burns

Inhalation injuries resulting from fires are uncommon in the lower airways and lung parenchyma, unless there is steam exposure. Chemical injuries to the respiratory tract depend on the chemical involved, the concentration of the chemical, its solubility and duration of exposure. Ammonia for example tends to dissolve in the upper respiratory tract and cause injury there but when the concentration is high or the exposure is prolonged, there may be damage to the lower respiratory tract as evidenced by our study of the 12 patients exposed to an ammonia tank explosion, when both the bronchoscopy and ventilation study showed abnormal findings in 9 of 12 patients.

Fibreoptic bronchoscopy, Xenon-133 lung scans and pulmonary functions tests have been useful objective tests in the diagnosis of inhalation burn injury [11}. Bronchoscopy is safe and accurate and it is possible to visualise larynx, trachea, carina and main stem and segmental bronchi. Xenon-133 lung scans are not available in our part of the world, and is expensive for us to use routinely; hence our decision to use ^{99m}Tc DTPA aerosol. Both the aerosol and the Xenon lung scan have the limitation of false positives and false negatives in patients with pre-existing lung disease, and if they are smokers. Our patients were healthy young persons who had no proven lung disease previousiy, though some of them in the ammonia burns group may have been smokers. The damage caused by the ammonia was probably worse than the efrects or smoking as proven by the bronchoscopy findings. Pulmonary function tests such as FEV1, and MEFV (maximum expiratory flow volume) were not done routineiy as it would have been difficult for most of these patients to cooperate. A previous study done at this hopital [11] did not show any correlation between severity of bronchoscopic changes and PaO_2 or the severity of the skin burn. The single false negative radioaerosol ventilation result was possibly due to this investigation being done one week after the bronchoscopy, while the single false positive was either due to effect of smoking, or due to the delayed bronchoscopy 5 days after the ventilation scan.

It would appear that the retention images produced to obtain an index of regional lung ventilation and damage, are not useful in most cases. Serial studies in a few patients with lung parenchymal damage from inhalation burns have shown progressive improvement, deterioration, or no change in regional ventilation and clearance times of the radioaerosol, as shown in Table 2. Most of the Koreans were flown back to Korea soon after the accident and hence it was not possible to get long-term serial studies.

Studies using the plain chest film after smoke inhalation [12], have pointed to bronchial wall thickening and subglottic oedema, as heralding more serious respiratory damage both to the upper airways and to the lung parenchyma. We have not been able to correlate the radioaerosol clearance times with the chest X-ray findings.

An increase in the rate of submicronic aerosol of ^{99m}Tc DTPA clearance from the lungs has been reported in normal persons breathing at high lung volumes [13], healthy cigarette smokers [10], patients with chronic interstitial lung disease [14] and in patients with adult respiratory distress syndrome [15] and in assessing lung damage in AIDS [16]. Hence there is a belief that measuring altered respioratory epithelial permeability using clearance rate of ^{99m}Tc DTPA radioaerosol is not spoecific enough for use in the clinical situation [17]. In otherwise healthy, particularly young patients with no pre-existing lung disease and who are non-smokers (as is often the case here), there is a useful role for simple radioaerosol studies in assessing the lung parenchymal damage from respiratory burns.

More recent studies [18] stress the need for early diagnosis of the inhalation burn so that adequate treatment may be instituted early. Our preliminary studies [19,20] indicate that there is a definite role for DTPA clearance study in suspected inhalation burns.

Chronic Obstructive Pulmonary Disease (COPD)

We used a non-diffusible tracer (^{99m}Tc (tin) colloid) to image the pattern of ventilation of the lungs in COPD, and compared the inhalation images to the perfusion images that were subsequently acquired using i.v. ^{99m}Tc macroaggregated albumin (MAA). In general, the study indicated that in COPD, there were matched ventilation and perfusion abnormalities, confirming that regional ventilation regulates regional perfusion. The deposition patterns of the inhaled aerosol also help in differentiating the nature of the COPD; from the study we noted that the aerosol deposition tended to be central in emphysema, and peripheral in bronchitis, though obviously there will be mixed patterns in some patients. It is possible that abnormal deposition patterns may be noted earlier than changes in chest X-ray.

The ^{99m}Tc DTPA clearance study was done in eight of these patients with COPD; there was no reduction in clearance T½. If at all the T½ was slightly increased, due in part to the central tracer deposition with poor clearance from this site. The mean T½ was 78 min which is close to our normal range. Previous studies have also shown that COPD per se does not cause an increase in the rate of ^{99m}Tc DTPA clearance [14].

In summary the radioaerosols are useful in producing inhalation images of the lung, and in studying pulmonary epithelial permeability in various types of lung pathology.

Summary

Ventilation lung scans have been performed using Xenon-133 gas, Krypton-81m, and more recently with radioaerosols using Technetium-99m DTPA or colloid aerosol, and technetium-99m carbon particles (technegas). Compared to gases, the radioaerosols remain in the lung for a longer time and this enables multiple views of the lung. Quantitative studies of alveolar-capillary permeability can also be done, using soluble tracers such as ^{99m}Tc DTPA. This report deals with clinical studies using radioaerosols in pulmonary embolism, and with imaging and quantitative clearance studies using ^{99m}Tc DTPA in patients with suspected inhalation burns, in smokers and glue-sniffers and in patients with chronic obstructive pulmonary disease (COPD).

In the normal volunteers, the time taken for 50% of inhaled ^{99m}Tc DTPA to be cleared from the lungs (T½) was 66 minutes±1SD of 12 min. The smokers had a mean T½ of 20 min±1SD 4 min. In the hard-core glue-sniffing group, the majority were smokers who had stopped smoking and glue-sniffing for periods varying from 1 day to 42 days and it was possible to note the changes in clearance times against period of abstinence.

In the patients with inhalation burns, besides the T½, restention images of uncleared ^{99m}Tc DTPA in the lungs were obtained to note regional differences, if any, in lung clearance arising from pulmonary epithelial damage; these patients showed increased rate of clearance (short T½) with mean T½ of 36 min±1SD of 11 min, while the retention images revealed regional lung damage in moderately severe inhalation burns. 24 patients with COPD had inhalation scans done with ^{99m}Tc tin colloid radioaerosol, and these images were compared with the perfusion lung scans done with ^{99m}Tc macroaggregated albumin (MAA); in general the perfusion images matched the defects noted in the inhalation scans. The ^{99m}Tc DTPA clearance rate in these patients was normal i.e. T½=78±14 min.

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