# Chapter 25

# NUCLEAR TECHNIQUES IN THE DIAGNOSIS OF LUNG DISEASES

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## Introduction

In the late 50's, George V. Taplin was studying the function of the reticuloendothelial system (RES) by injecting aggregated particles of $^{131}$I-human serum albumin. The RES is dispersed over many organs but is concentrated predominantly in liver, spleen and bone marrow. It has the important function of removing undesirable particulate substances from the circulation. Because particles of less than 0.5 to 1.0 $\mu$m in size are taken up by the cells of the RES he was measuring the disappearance rate of the injected particles from the general circulation and the gradual build-up of radioactivity in the RES cells (Kupffer cells) of the liver. For some reason or other, his laboratory on one occasion mistakenly made particles about 100 times larger than usual. Some impulse made him inject these mistakenly made larger particles into experimental animals to find out organs in the body in which they were trapped. Naturally the first capillary network, that the particles encounter after an intravenous injection is that in the lungs, and he found that most of the particles were, indeed, trapped there. The smaller particles were taken up by the RES cells of the liver. When a gamma ray scan was made, the mapping of the trapped radioactive particles showed up as images of the lungs and the liver. Working on this basis, Taplin developed a method of producing suitable sized albumin aggregates for lung imaging that would be safe for human use. He named them $^{131}$I-MAA (macroaggregated human serum albumin). Because many fruitless endeavours had been made to find a lung imaging agent to facilitate the diagnosis of pulmonary embolism in early 60's, this serendipitous creation of $^{131}$I-MAA was widely welcomed as the best and the only agent for perfusion lung imaging as soon as his first report was published in 1963.

Nobody would have thought, however, that his fortuitous production of $^{131}$I-MAA in 1963 and his subsequent proposal of aerosol inhalation lung imaging in 1965 would revolutionize and widen the scope of pulmonary medicine to the extent that we enjoy today. Regarding aerosol inhalation lung imaging Pircher's contribution should not be forgotten, because he and his co-workers also proposed aerosol inhalation lung imaging almost simultaneously and independently.

Perfusion and inhalation lung imaging have not only facilitated the diagnosis of pulmonary embolism but also made it possible to see respiratory and non-respiratory lung function. The contribution of nuclear techniques to pulmonary medicine is immense and has been briefly outlined in the following pages.

CHAPTER 25

# I. RESPIRATORY LUNG FUNCTION

## 1. Perfusion lung imaging

Lung function consists of pulmonary arterial perfusion, ventilation and diffusion of oxygen and carbon dioxide between perfusion and ventilation. Perfusion is equivalent to the distribution of the pulmonary arterial blood flow in the lungs that has returned from the entire body carrying the venous blood. The venous blood is to be replenished with oxygen in the lungs before being sent to the systemic circulation. Ventilation is the distribution of inhaled gas in the lungs to supply oxygen to the venous blood and remove carbon dioxide from it through diffusion. This process of gas exchange is called "respiration" **(Fig. 25.1)**.

### 1. How to study perfusion distribution in the lungs?

Currently $^{99}Tc^{m}$-MAA is used as a tracer for perfusion lung imaging instead of $^{131}I$-MAA. The size of $^{99}Tc^{m}$-MAA ranges from 15 to 50 $\mu$m and is slightly larger than the red blood cells. Once slowly injected intravenously they are mixed in the right heart chambers and carried to the lung precapillary and capillary networks where they are trapped **(Fig. 25.2)**. It shows perfusion and inhalation aerosol deposition in the lungs in a normal subject. The latter, in normal subjects, is equivalent to ventilation distribution in the lungs.

*(a) Body position*

Because the lung is like a manometer, if a tracer is injected with the subject in the sitting position, the distribution of radioactivity represents the perfusion distribution in the lungs in the sitting position. If the tracer is injected in the supine position, the distribution of radioactivity represents the perfusion distribution in the lungs in the same supine position. In the sitting position, the lower lung regions show more perfusion per unit lung volume than the upper lung, but in the supine position, little difference exists in the distribution of perfusion between the upper and the lower lung fields. This is the "gravity effect" on perfusion in the lungs. If a tracer is injected with the subject in the right or left lateral position, the lower-positioned lung shows more perfusion distribution than that lung in either the supine or the sitting position due to the gravity effect. This is an important physiological fact that should be borne in mind in interpreting perfusion lung images.

*(b) Lung volume*

Perfusion distribution at different lung volumes can be studied if a tracer is injected at the lung volume determined by respective respiratory positions such as the residual volume (RV) or the total lung capacity (TLC) level. The perfusion distribution seen routinely in lung imaging is usually obtained at the lung volumes of resting tidal ventilation.

*(c) Radioactive gases*

Similar studies can be done using radioactive gases such as $^{133}Xe$ (xenon) and $^{81m}Kr$ (krypton) dissolved in saline and 5 % glucose solution, respectively. Breath-holding is required not only when the radioactive solution is injected but also when the lungs are being imaged. Otherwise radioactive gases would be exhaled from the lungs. Only one projection of the lungs is imaged at one time. In other words when the lungs are imaged from anterior, posterior and both right and left lateral projections, four injections are necessary and breath-holding is required each time. This is not practical. Usually better lung perfusion images with better statistics are obtained with $^{99}Tc^{m}$-MAA than with radioactive gases.

*(d) Multiple projections*

Usually four view perfusion lung images are taken; anterior, posterior, right and left lateral views. Additional views like right and left anterior oblique or respective posterior oblique projections are taken if required.

## 2. Pathological factors influencing perfusion distribution in the lungs.

*(a) Vascular obstruction*

In pulmonary embolism blood clots (thrombi) obstruct the vascular lumen and the blood flow cannot pass through it. Lung regions distal to the obstruction has diminished or absent perfusion. **(Fig. 25.3)**.

*(b) Parenchymal lung disease*

In pneumonia, lung abscesses, tuberculosis or any parenchymal lung disease, vascular beds are involved in the disease processes to the extent that pulmonary arterial blood flow cannot pass through the vascular channels in the pathological region and, as a result, the regional perfusion is disturbed. In addition to structural changes in the vascular beds in parenchymal lung diseases, once the alveoli are filled with liquid or cellular material such as purulent discharge or cell debris, regional hypoxia ensues and the perfusion becomes diminished or absent there due to hypoxic vasoconstriction as described below.

*(c) Vascular compression and/or invasion*

In bronchogenic carcinoma, the pulmonary arterial beds are extrinsically compressed or invaded so that the perfusion is diminished or absent distal to the compression or invasion. In sarcoidosis pulmonary perfusion is not usually affected.

*(d) Vascular stenosis or agenesis*

In congenital pulmonary vascular anomaly like pulmonary artery stenosis, the perfusion distal to the stenosis can be diminished or absent. In pulmonary artery agenesis, there is no vascular channel for the blood to flow.

*(e) Alveolar hypoxia (low oxygen tension).*

In primarily obstructive airway diseases like pulmonary emphysema **(Fig. 25.4)**, bronchitis, bronchial asthma, panbronchiolitis, bronchiectasis, the perfusion is also decreased. Distal to bronchial obstruction due to intraluminal tumours or foreign substances such as a swallowed foreign body, perfusion is diminished or absent. In pulmonary emphysema, vascular destruction is associated with alveolar wall destruction and stretching of the vascular beds may contribute to the decrease in perfusion but alveolar hypoxia is the commonest cause for changes in perfusion in all these diseases.

Experimentally when hypoxic gas is inhaled, perfusion in the lung region is diminished due to hypoxic vasoconstriction or vascular narrowing. The same phenomenon is observed when ventilation is interrupted. In other words, the oxygen tension in the alveoli has been found to be the most important factor in regulating regional perfusion distribution. This physiological reaction can take place promptly in any of the regions in the lungs. Regional hypercapnia (high carbon dioxide tension) does not seem to contribute to such a hypoperfusion (decreased perfusion).

**3. Pulmonary Embolism**

In pulmonary embolism, parts of the pulmonary arterial system are blocked by thrombi so that pulmonary perfusion is absent in the regions distal to the thrombi **(Fig. 25.3)** and the gas exchange is impaired. Patients suffer from shortness of breath and chest pain. Unless the diagnosis is made promptly and the treatment started, it is usually a fatal condition.

Shortness of breath, chest pain, and bloody sputum are cardinal symptoms, but they are common to many other lung diseases that the clinical symptoms and signs are not in themselves helpful in diagnosing pulmonary embolism. Unfortunately chest x-rays cannot reveal the presence of emboli or underlying subtle vascular changes. Only pulmonary angiography using contrast media can show filling defects or narrowing of the vascular lumen, but angiography itself is not without risks. Perfusion images when combined with ventilation images (either with radioactive gases or radioaerosols) are indispensable to the diagnosis of pulmonary embolism, because in pulmonary embolism ventilation is not disturbed in embolic regions where perfusion is absent.

By taking multiple view lung perfusion images, naturally in areas distal to a blockade caused by emboli little perfusion is present and little radioactivity is seen as shown in **Fig. 25.3.** It is because of the simplicity of the technique that lung perfusion imaging with $^{131}$I-MAA and now $^{99}Tc^{m}$-MAA has enjoyed a wide acceptance. Diagnosis of pulmonary

embolism, even in emergency situations, is greatly facilitated by perfusion lung imaging. When done in tandem with radioaerosol inhalation lung imaging the sensitivity and the specificity for the diagnosis of pulmonary embolism is close to 100 %. Physiologically speaking, bronchoconstriction and hypoventilation can occur immediately after blockage of pulmonary arterial blood flow, but this phenomenon is transient and is known to disappear in dog experiments within six hours. Under clinical situations, six hours would have already passed before a doctor is ready to do the lung imaging.

Preoperative perfusion lung imaging is very helpful when a patient postoperatively develops symptoms and signs suspicious of pulmonary embolism. By comparing the preoperative and postoperative perfusion images in patients in whom pulmonary embolism is suspected, diagnosis of pulmonary embolism is greatly facilitated without doing inhalation lung images.

## 4. Perfusion Abnormalities in Other Lung Diseases

As mentioned earlier, regional perfusion can be reduced or absent, not only in pulmonary embolism, but also in parenchymal lung diseases and in airways diseases.

Besides the anatomical changes in the pulmonary vasculature, the lung perfusion is regulated by the alveolar oxygen tension. Ventilatory disturbances result in regional alveolar hypoxia which, in turn, constricts the regional pulmonary arterial beds to reduce the blood flow there. A regional decrease in perfusion ensues as soon as regional hypoxia takes place.

Parenchymal lung diseases can be recognized by chest X-rays as an area of increased density, but differentiation of pulmonary embolism or vascular diseases in general from airways disease by chest X-rays is usually extremely difficult. Here arises the importance of studying lung perfusion in conjunction with ventilatory function.

## 5. Assessment of Regional Lung function

It has been observed that the distribution ratio of the injected MAA in the right and left lungs corresponds closely with the oxygen consumption ratio. Perfusion lung imaging is, therefore, not limited to the diagnosis of pulmonary embolism as originally envisaged, but also offers a new means of studying regional pulmonary function. Obviously lung function or gas exchange cannot exist without perfusion. Where in the lungs the function is preserved? An answer to this question is vital when considering various alternatives for the treatment of the patient. The actual sites of poor or absent perfusion can be shown and quantitated by this simple, safe and non-invasive perfusion lung imaging procedure.

In countries like Japan where the incidence of pulmonary embolism is extremely low, perfusion lung imaging is widely used to study regional lung function. Before a lung operation, for example, perfusion lung imaging and the quantitative determination of the

perfusion ratios in the right and left lungs are essential for the evaluation of regional pulmonary function. Perfusion lung imaging by nuclear techniques has completely replaced complicated invasive procedures for preoperative lung function evaluation.

### 6. Safety of perfusion lung imaging

Because MAA particles are intravenously injected and trapped in the lung precapillaries and the capillary beds, the fear that MAA injection itself might be hazardous, causing microemboli in the pulmonary vascular beds is reasonable and understandable. Actually in the '60s when the MAA particles were not commercially available and made by the user in his own laboratory, there were indeed several accidents because the injected particles often contained particles larger than 150 $\mu$m in diameter. There were other reported incidents of adverse reactions in patients with severe pulmonary hypertension.

Human lungs have about 300 million arterioles and 380 billion capillaries. If we assume that 5 mg of MAA, containing 0.8 million particles whose sizes are smaller than 20 $\mu$m in diameter and 0.2 million particles whose sizes are over 20 $\mu$m, is injected, the possibility of blockade is in 1 in 35 000 capillaries and one in 1500 arterioles or precapillaries. Usually less than 1 mg of MAA is injected and the safety margin is much greater than this assumption. Taplin reported that if the particles are less than 35 $\mu$m in diameter, there is absolutely no haemodynamic effect either on the systemic or the pulmonary circulation even after injecting 40 mg of MAA per kg body weight in the dogs. When the particle size is larger than 80 $\mu$m, injection of 25 mg of MAA per kg of body weight can cause depression of the systemic blood pressure and elevation of the pulmonary artery pressure. In this sense, MAA is one of the safest radiopharmaceuticals and the fear about its safety is unjustified. MAA can be practically used in any patient without any kind of apprehension. Making MAA preparation in one's hospital radiopharmacy should be undertaken only if strictest quality control is possible.

## 2. VENTILATION LUNG STUDIES

Both radioaerosols and radioactive gases such as $^{133}Xe$ and $^{81}Kr^{m}$ can be used for studying ventilation distribution in the lungs (**Fig. 25.2**). Aerosols are appropriate for taking multiple views following the inhalation, whereas gases are more suitable for studying the dynamic aspect of ventilation.

### 1. How to study ventilation in the lungs?

*(a) Radioactive gases*

(i) Single breath method

In practice the single breath method is most frequently used; radioactive gases are inhaled from the residual volume (RV) to the total lung capacity (TLC) levels by a single breath and

then the breath is held for 10 sec or so followed by breathing air. Then the inhaled radioactive gases are washed out.

(ii) Tidal breathing method

Instead of inhaling radioactive gases in a single breath, tidal breathing is done from a container of radioactive gases. At a certain point the circuit is switched to breathing air following a breath-holding period and radioactive gases are washed out.

(iii) Equilibration method

Radioactive gases are inhaled from a container in a closed circuit from a given respiratory level such as the RV or the functional residual capacity (FRC) to the total lung capacity (TLC) level and the breath is held to determine the distribution of ventilation in the lungs. Then the subject keeps breathing the radioactive gases until an equilibrium state of radioactivity is reached between the whole circuit and the subject's lungs and then holds his or her breath at the TLC level to determine the lung volume. Then the circuit is switched open to permit breathing air and the washout phase is recorded. $^{81}Kr^{m}$ gas is not suitable for this kind of study because of its short physical half life. In all the above methods the exhaled gases need to be collected.

*(b) Radioaerosols*

Radioaerosols are inhaled in resting tidal breathing until radioactivity, enough for a good image, deposits in the lungs. For this purpose, deposition of, at least, one to two mCi in the lungs is necessary. The radioaerosol inhalation imaging shows the distribution of the deposition of the radioaerosols in the lungs. The main purpose of the aerosol studies is to know whether or not the regions of interest in the lungs are aerated and how aerosols deposit in these regions as well as in the entire lungs. If inhaled aerosols deposit in the lung regions, that means that the ventilation is present there.

Radioaerosols are generated either with jet nebulisers or with ultrasonic nebulisers. They are commercially available and those that consistently produce particle size less than 3 $\mu$m in mass median diameter, are acceptable for clinical use. **Table I** shows the size of aerosol particles produced by various aerosol generators. As described later, BARC(Bhabha Atomic Research Centre) nebuliser, a jet nebuliser made by assembling needles, test tube and an air compressor, originally developed in India is quite good for routine use and can be even fabricated in one's own laboratory. The Appendix I shows a construction diagram of the BARC nebuliser.

TABLE I. MASS MEDIAN DIAMETER (Dm) AND GEOMETRIC STANDARD DEVIATION ($\sigma$g) UNDER STANDARD CONDITIONS (TEMPERATURE 37°C, RELATIVE HUMIDITY: 100%, AND TEST AGENT: $^{99}Tc^{m}$-ALBUMIN) MEASURED BY CASCADE IMPACTOR (ANDERSEN SAMPLER)

| NEBULIZER | Dm ($\mu$m) | $\sigma$g |
|---|---|---|
| Jet Nubulizers | | |
| OEM-1 (USA) | 1.96 | 1.65 |
| OEM-2 (USA) | 1.19 | 1.86 |
| Ultravent (USA) | 1.04 | 1.71 |
| Penicillin nebulizer glass (Japan) | 1.76 | 1.70 |
| BARC with reservoir (India) | 0.84 | 1.73 |
| BARC without reservoir | 1.57 | 1.80 |
| Ultrasonic nebulizers | | |
| Mistogen EN-142 (USA) | 1.93 | 1.52 |
| Omuron-NE-U11 (Japan) | 1.62 | 1.50 |
| Devilbiss (USA) | 1.78 | 1.60 |

## 2. Significance of ventilation studies

Ventilation is usually disturbed in various parenchymal and chronic obstructive lung diseases but not affected in vascular diseases such as pulmonary embolism.

In a region of the lung where the ventilation is primarily disturbed, washout (disappearance rate) of inhaled radioactive gases is prolonged, and radioactivity remains longer in the affected region than in the healthy regions of the lungs.

An image of the distribution of inhaled aerosols is not, strictly speaking, an image of the ventilation in the lungs especially in the presence of complicated obstructive airways disease. The word "inhalation imaging" is more appropriate than "ventilation imaging". With radioaerosol imaging, only the deposition of the inhaled particles in the lungs is seen, as there is no washout as in the case of gases. Despite this limitation, aerosol deposition patterns are helpful in distinguishing the lung regions with good ventilation from the regions which are poorly ventilated. They are also useful in diagnosing the nature of the underlying disease. Whereas a central deposition pattern indicates an emphysematous type of obstructive airways

disease, non-homogeneous or peripheral patchy distribution suggests a bronchitic type of disease. Most patients with obstructive lung diseases, however, show both kinds of patterns combined in different proportions (**Fig. 25.5**).

### 3. Agents used for ventilation studies

Except for ultra-short half-life radioisotopes produced by the cyclotron, $^{133}Xe$ and $^{81}Kr^{m}$ are exclusively used as radioactive gases for ventilation studies. Radioactive gases for inhalation are mixed with either air or oxygen.

Agents used for radioaerosol production are $^{99}Tc^{m}$-albumin, $^{99}Tc^{m}$-DTPA, or $^{99}Tc^{m}$-phytic acid. The aerosols are produced with either an ultrasonic nebulizer or a jet nebulizer. In addition to the airflow rate and the shape of the airways, the size of inhaled aerosols is an important factor in determining the aerosol distribution in the lungs. The size of aerosols is different with different instruments as shown in **Table I.**

### 4. Combined Perfusion and Inhalation Lung Imaging

Images of the distribution of inhaled radioaerosols or radioactive gases give a good idea of the ventilatory status and the degree of functional disturbance in the lungs. A comparison of inhalation lung studies with perfusion images can show how well regional perfusion matches with regional ventilation. If ventilation is present in non-perfused regions in patients with normal chest X-rays, those lung regions can be diagnosed as having some kind of vascular diseases including pulmonary embolism (**Fig. 25.3**). If perfusion is absent or abnormal in lung regions where inhalation studies also show evidence of abnormal ventilation, those lung regions are diagnosed as having some kind of airways disease where alveolar hypoxia has induced regional perfusion abnormalities by hypoxic vasoconstriction (**Figs. 25.6 and 25.7**).

It is clear from this that lung imaging is not complete without images of both the perfusion and the ventilation systems. Obtaining the latter is difficult in many developing countries because of the unavailability of the labelled gases. The use of radioaerosols now makes it possible to do total lung imaging in these countries and diagnose many acute and chronic disorders of the lungs.

In a co-ordinated research programme (CRP) sponsored by the IAEA over the period of 1987-1990 to promote lung imaging in developing countries, a jet nebulizer originally developed at Bhabha Atomic Research Centre (BARC) in India has been used in ten countries in the Asia and Pacific region. The nebulizer contains a series of hollow needles and a compressed air pump. As shown in **Table I**, the mass median diameter of aerosol produced by the BARC nebulizer was 0.84 um with geometric standard deviation of 1.73, if the nebulizer is used with a reservoir placed between the aerosol generating part and the mouth piece. The size of aerosol produced by BARC nebulizer is appropriate for studying the distribution of inhaled aerosols in the lungs as a simulation of ventilation distribution. Both $^{99}Tc^{m}$-DTPA and $^{99}Tc^{m}$-albumin can be used to prepare radioaerosols in this kind of nebulizer.

Once the aerosols are inhaled and imaged, injection of three to five times as much $^{99}Tc^{m}$-MAA can follow to give simultaneous perfusion images. Normally, except in emergency situations, perfusion imaging is done initially and is followed 24 hours later by aerosol inhalation lung studies.

Recently an instrument called "Technegas" has been developed in Australia. This produces an aerosol less than 200 nm in size. The principle of the aerosol generation is as follows; a carbon crucible that has adsorbed $^{99}Tc^{m}O_4^-$ is instantly heated to 2500 degrees in the atmosphere of argon (Ar) gas and $^{99}Tc^{m}$ tagged carbon particles are generated. Inhaled aerosol penetrates better to the lung periphery than conventional aerosols generated ultrasonically or by jet nebulizers and the alveolar deposition ratio is about 85 %, while it is about 40-50 % with the inhaled aerosol generated by ultrasonic and jet nebulizers.

## III. NON-RESPIRATORY LUNG FUNCTION

Apart from ventilation and perfusion, a lung function that has nothing to do with gas exchange or respiration can also be studied by using aerosols **(Fig. 25.8).** They are mucociliary clearance function, pulmonary epithelial permeability and few other non-respiratory lung functions.

### 1. Mucociliary Clearance Function.

Mucociliary clearance is the first line of defense of the lungs against undesirable material inhaled inadvertently. How to measure and evaluate mucociliary transport and clearance mechanism has been a long-standing problem. A nuclear technique has solved this problem to some extent and mucociliary clearance function can now be studied by inhalation of radiolabelled aerosols. Nuclear methodology has revealed what the mucociliary clearance mechanism is like in vivo. What it involves is a sequential measurement of the distribution of inhaled aerosols in the lungs over a period of time and analysis and comparison of the changes in radioactivity in the sequential images.

Bronchial mucus is transported upwards toward the larynx by the interaction of the mucous layer and the ciliary beating motion in order to get rid of:

(a) mucus itself
(b) intrinsically produced cell debris,
(c) extrinsically inhaled particulates and
(d) chemical substances dissolved in the mucus so that the lungs and the airways are kept clean.

In pathological conditions, this upward transport has been found to be disturbed in various ways.

Mucociliary clearance takes place only on the ciliated airways but inhaled aerosols deposit not only on the ciliated airways but also on the non-ciliated airways and the alveolar space. Thus radioactivity deposited in the non-ciliated airways should be excluded from the evaluation of mucociliary clearance function. The radioactivity remaining in the lungs at 24 hrs after the inhalation is defined as the radioactivity deposited in the non-ciliated airways including the alveoli. Aerosols deposited in the non-ciliated airways including the alveoli, are cleared by other mechanisms than mucociliary clearance. Macrophages play an important role in clearing aerosols that deposit in the non-ciliated space of the lungs. In order to separate the non-ciliated portion of the lungs including the alveolar space from the ciliated airways, the percentage of the net radioactivity in the lungs at 24 hours after inhalation of aerosols ( minus the body background ) versus the total initial radioactivity is defined as alveolar deposition ratio (ALDR). The following parameters are also defined and calculated as shown in **Fig. 25.9**: lung retention ratio (LRR), airway deposition ratio (ADR), airway retention ratio (ARR), airway clearance efficiency (ACE) and ALDR. Using radioaerosol of mass median diameter of 1.93 um with geometric standard deviation of 1.52, the ALDR can be calculated by the following formula:

$$\mathbf{ALDR(\%) = -48.08 + 0.47 \times FEV_{1.0}\% + 0.59 \times LRR60.}$$

Here $FEV_{1.0}\%$ is forced expiratory volume in one second divided by forced vital capacity in % and LRR 60 is lung retention ratio LRR) at 60 min in %. In addition to the ALDR and the LRR, airway deposition ratio (ADR), airway retention ratio (ARR) and airway clearance efficiency (ACE) are calculated to quantitate the mucociliary clearance function in the lungs. These ratios would differ according to the size of aerosols inhaled.

The mucociliary clearance mechanisms can be visualized by a cinematographic display of sequential images of the lungs after aerosol inhalation. This procedure is called " radioaerosol inhalation lung cine-scintigraphy ". In normal subjects, the mucus flow is steady and cephalad in direction, but in pathological states four main abnormal transport patterns are seen;

(i) stasis or a transient stopping and starting of mucus globs in the airway,

(ii) regurgitation or a retrograde transport of mucous globs in a reverse direction to the original site,

(iii) straying of mucus globs to either the ipsilateral or the contralateral lungs and

(iv) zigzag or spiral path of mucus transport **(Fig. 25.10)**.

In lung diseases like obstructive airways disease, bronchogenic carcinoma, or bronchiectasis, all the four above abnormal transport patterns are seen to a varying degree. In pulmonary vascular diseases, mucus clearance function is well preserved without abnormal transport patterns, unless obstructive lung disease is also present concurrently.

Studies using this technique have shown, for example, that beta 2-stimulators do not facilitate mucus transport as widely suggested by commercial advertisements. However, their pharmacologic action as bronchodilators can be definitely confirmed by radioaerosol inhalation lung imaging.

## 2. Pulmonary epithelial permeability

The aerosol $^{99}Tc^{m}$-DTPA, a small molecular chelating substance, disappears from the lungs rapidly after inhalation. It is not yet well understood how it is cleared from the lungs, but it is now accepted that measurement of its clearance rate from the lungs can serve as a test of pulmonary epithelial permeability. Smoking and interstitial lung diseases make it easier for the inhaled aerosols to pass through the pulmonary epithelial membrane and the half time of clearance (T½) becomes shorter. **(Fig. 25.11)**. The technique provides dramatic evidence of damage caused by smoking for periods as short as few weeks, even before the subject has any symptoms. The T½ becomes shorter when patients develop interstitial pneumonitis induced by radiation therapy or drugs and lengthens when this condition improves.

$^{99}Tc^{m}$-HMPAO (hexamethylpropylene amine oxime) which is a lipophilic $^{99}Tc^{m}$-complex (MW 380), normally used for measuring cerebral blood flow, can also be used as aerosols and its disappearance seems to be related to the degree of pulmonary epithelial damage.

Pulmonary vascular permeability instead of pulmonary epithelial permeability can be studied by measuring radioactivity in the lungs following injection of radioactive albumin solution.

## 3. Other Radiopharmaceuticals for lung studies

### *(a) $^{123}$I-IMP ($^{123}$I-Iodoamphetamine)*

The agent $^{123}$I-IMP is used to study cerebral blood circulation. When it passes through the lungs following intravenous injection, a significant portion of it is retained in the lung. Whether it reacts with "amine receptors" in the lungs is not yet established but it seems to have some affinity for the endothelial cells especially when they are damaged. Clearance of radioactivity is delayed from the lung areas where pulmonary arterial perfusion is disturbed. The true significance of its lung retention is not clear but suggests that some kind of non-respiratory lung function, probably affecting the pulmonary vascular beds, is the cause. This problem needs further study, but unfortunately this radiopharmaceutical is not likely to be easily available in the developing countries.

### *(a) $^{67}$Ga-citrate ($^{67}$Gallium-citrate)*

This agent was first developed as a tumour imaging agent. Indications for the gallium scan for some types of tumour are clear, but for other types its use is debatable. A positive uptake is seen in a wide range of benign lung conditions such as infections, interstitial lung

diseases, sarcoidosis, pneumoconiosis, and interstitial fibrosis. In interstitial lung diseases, radioactive uptake in the lung increases initially when it is active and decreases when the disease process is slowed down or stabilized. Again, it is not clear where in the lungs this agent is picked up, and most of the diagnostic information that it provides is non-specific in nature. It is also relatively expensive and not easy to obtain in the developing countries.

## FUTURE PROSPECTS

With the help of nuclear techniques not only respiratory but also certain non-respiratory functions can be investigated and functional images of the lung can be obtained from which lung function can be analyzed in quantitative and dynamic terms both globally and regionally in the lungs. Further exploration is needed to extend the coverage to the metabolic or biochemical aspects of non-respiratory functions of the lungs.

Lung studies by nuclear techniques have been mostly neglected so far in the developing countries because " total lung imaging " was not possible. The availability of radioaerosols had now provided means to do complete lung studies in these countries. IAEA's effort to make radioaerosol techniques more widely available in the Asian countries has been most noteworthy.

Pulmonary tuberculosis is still prevalent in the developing countries, scourge of smoking is becoming increasingly wide spread and atmospheric pollution is on the rise as these countries race towards industrialisation with insufficient technical and financial resources. These conditions would provide a fascinating backdrop of infective, cancerous and pollution-induced conditions of lungs where lung imaging techniques would have a large scope of providing useful service.

Present day lung imaging can show the ravages of a disease process by visualizing the state of perfusion, ventilation and certain aspects of non-respiratory functions but does not always indicate a specific disease. For example, a "coin lesion" due to either tuberculosis or lung cancer produces very similar findings. Even if a small abnormality is found on chest X-ray pictures, and even if malignancy is highly suspected on the basis of all other investigations, the definitive diagnosis is often elusive, because no pathologic material is accessible by any of the non-invasive methods. However, there is now hope for a specific diagnosis of lung cancer or malignancy in general by nuclear medicine techniques. It has become possible to produce, at least in vitro, "cancer specific" monoclonal antibodies. If a lesion could be diagnosed as malignant by nuclear imaging using radiolabelled monoclonal antibodies in vivo, the benefits would be invaluable.

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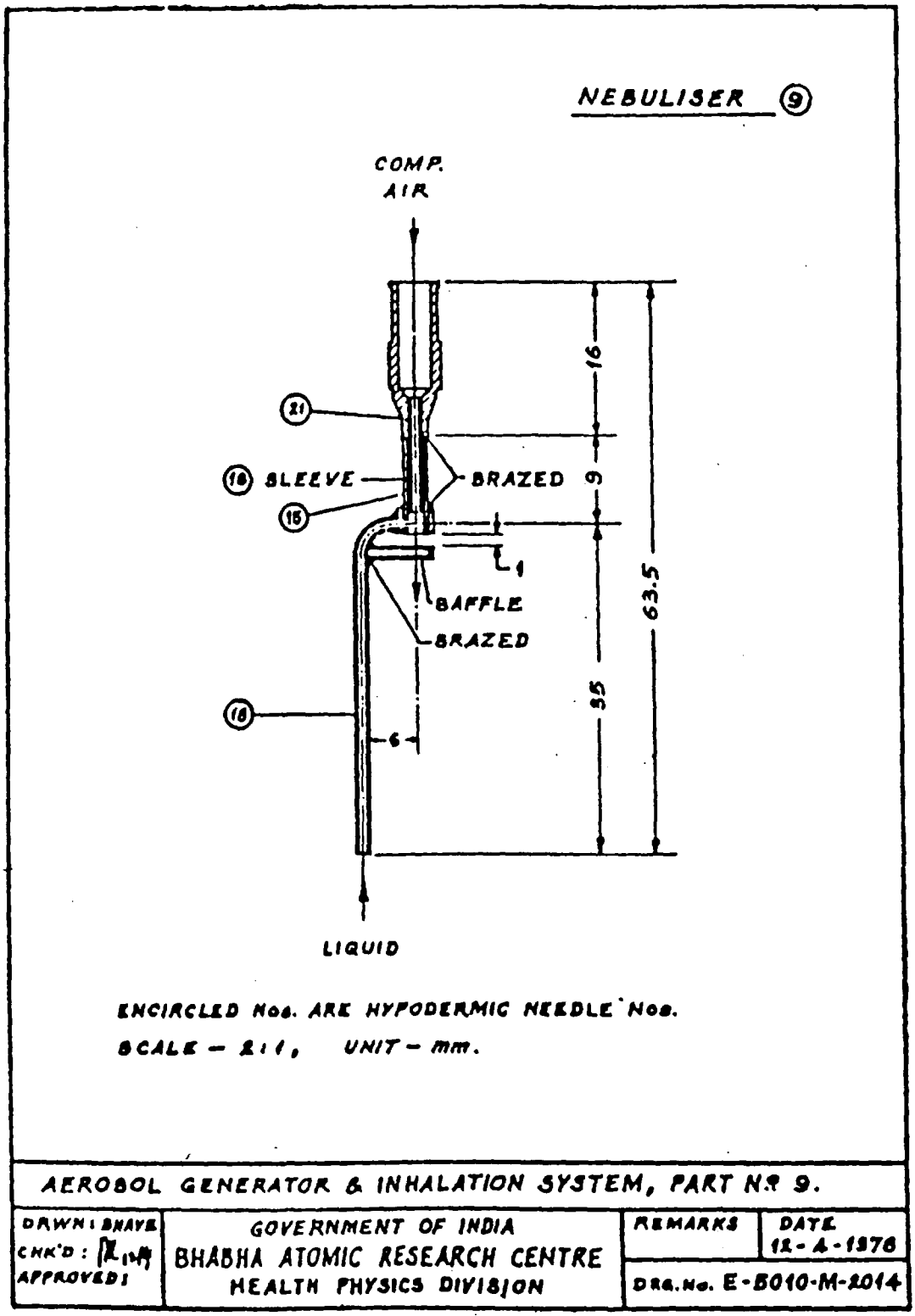
## Appendix I


NEBULISER (9)
COMP. AIR
(21)
(18) SLEEVE
(15)
BRAZED
16
9
63.5
35
BAFFLE
BRAZED
(18)
6
LIQUID
ENCIRCLED Nos. ARE HYPODERMIC NEEDLE Nos.
SCALE – 2:1, UNIT – mm.
AEROSOL GENERATOR & INHALATION SYSTEM, PART No. 9.
DRWN: BHAVE
CHK'D:
APPROVED:
GOVERNMENT OF INDIA
BHABHA ATOMIC RESEARCH CENTRE
HEALTH PHYSICS DIVISION
REMARKS
DATE 12-A-1976
DRG. No. E-5010-M-2014

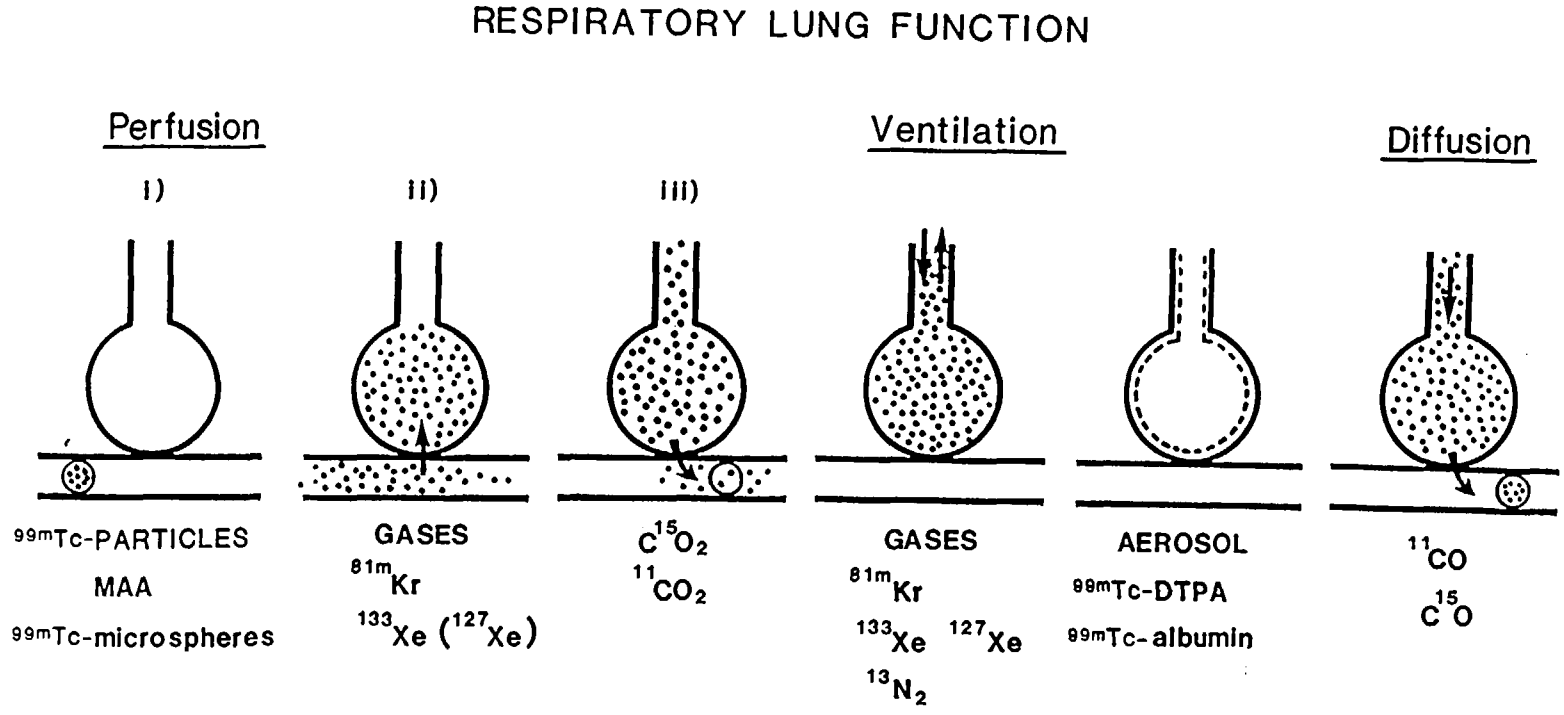



**Fig. 25.1** Schematic diagrams of various respiratory functions and radionuclides used for studying them.

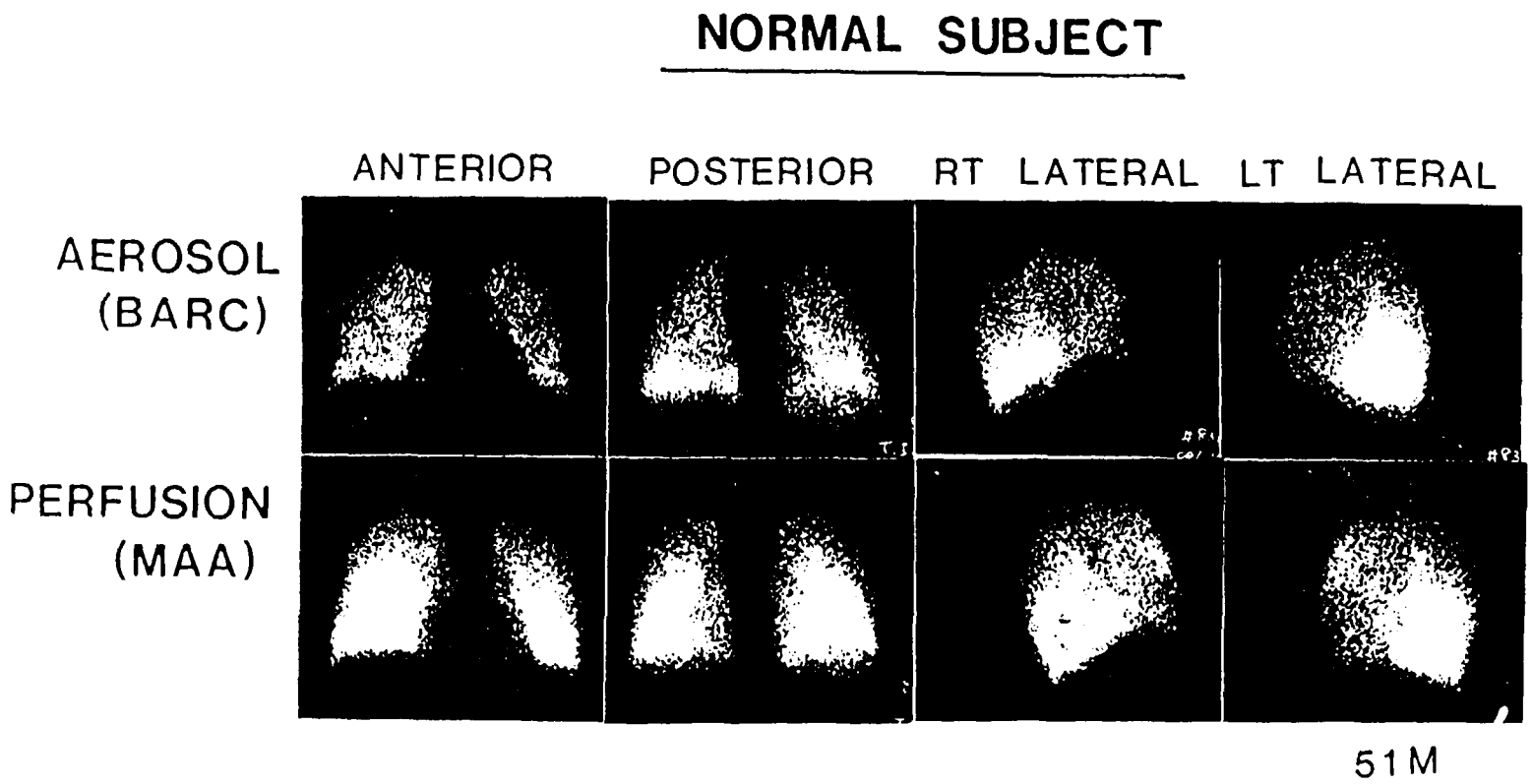



**Fig. 25.2** A 51 year old normal subject. Radioaerosol inhalation (upper row) and perfusion (lower row) lung studies in anterior, posterior, and right and left lateral views. Practically no distinction can be made between aerosol inhalation and perfusion lung images in any of the four projections.

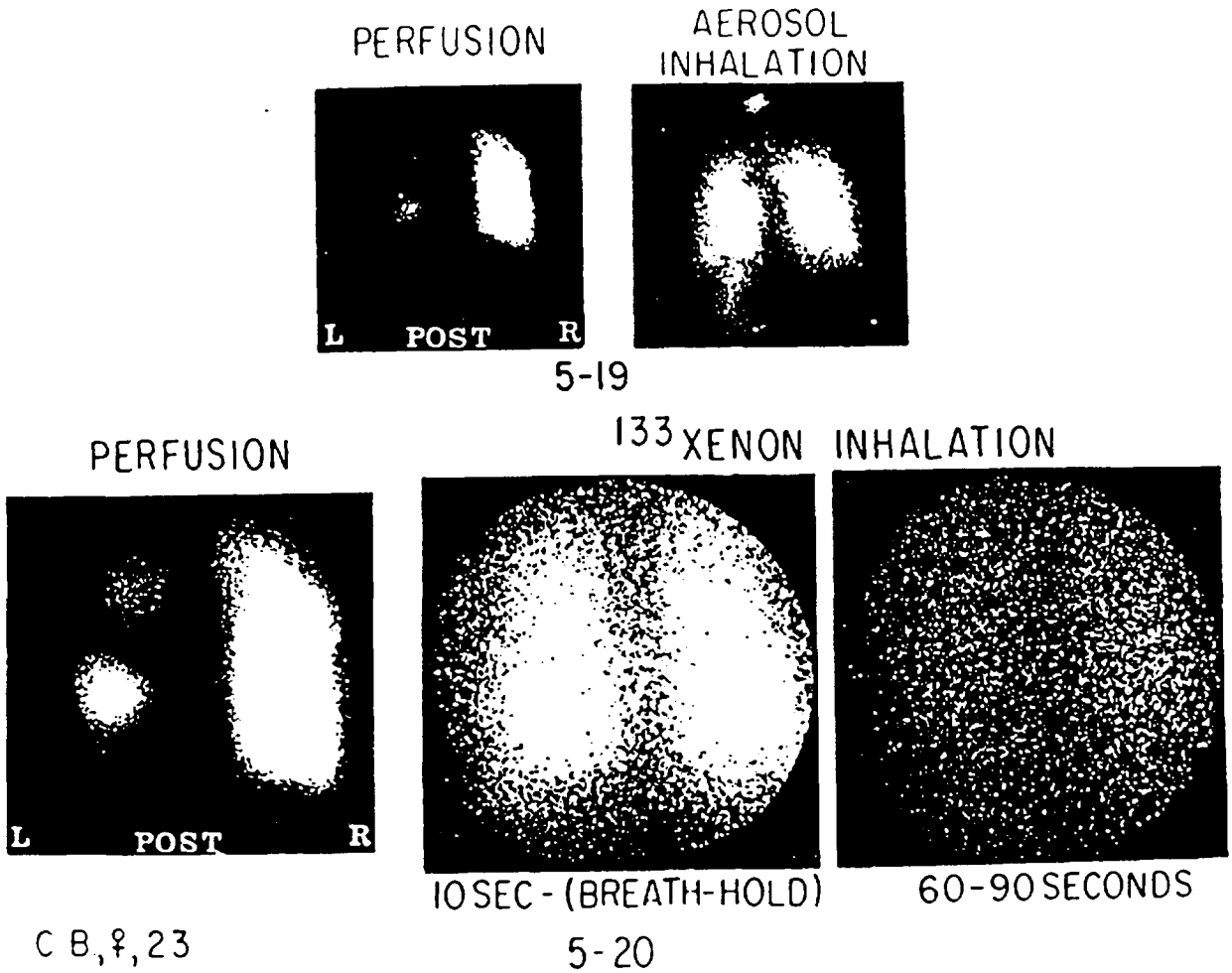



**Fig. 25.3** A 23 year old woman with massive pulmonary embolism in the left lung. Posterior perfusion, and radioaerosol inhalation lung images (upper row) studied on May 19, and posterior perfusion and xenon inhalation (breath-bold) and washout images (lower row) studied on the following day (May 20). In the left lung where perfusion is greatly diminished, inhaled aerosol deposits normally. Inhaled xenon gas distributes homogeneously by single breath method. Furthermore no evidence of xenon gas retention can be detected in either lung, especially in the left lung during the washout phase, indicating the presence of normal ventilation without bronchoconstriction in the embolic left lung.

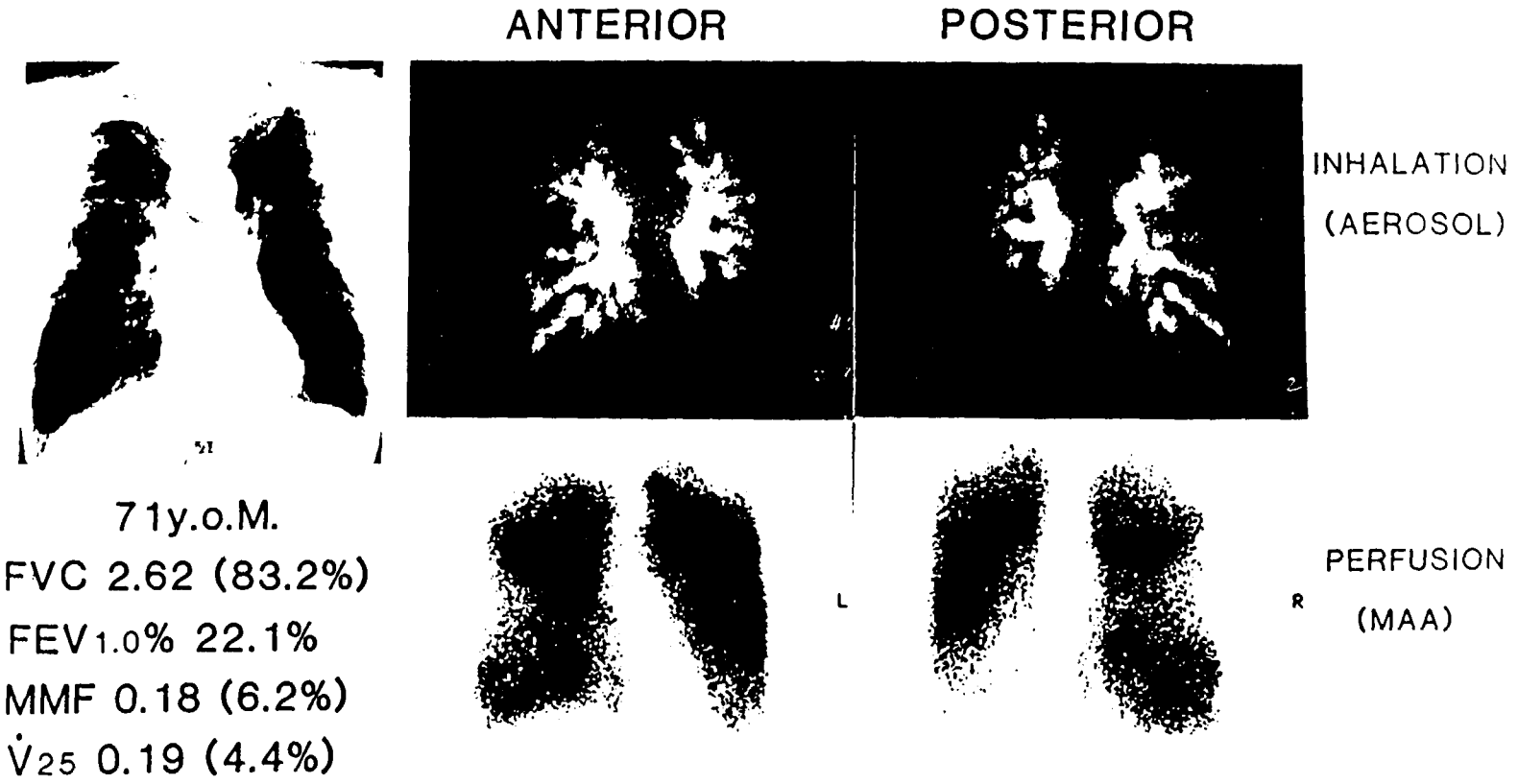



**Fig. 25.4** Perfusion and radioaerosol inhalation lung images in a 71 year old patient with chronic obstructive pulmonary disease. Note inhomogeneously decreased perfusion in the right and left lungs and excessive deposition of inhaled aerosol in the large airways (central pattern) and patchy inhomogeneous deposition in the peripheral lungs, making mixed central and peripheral pattern.

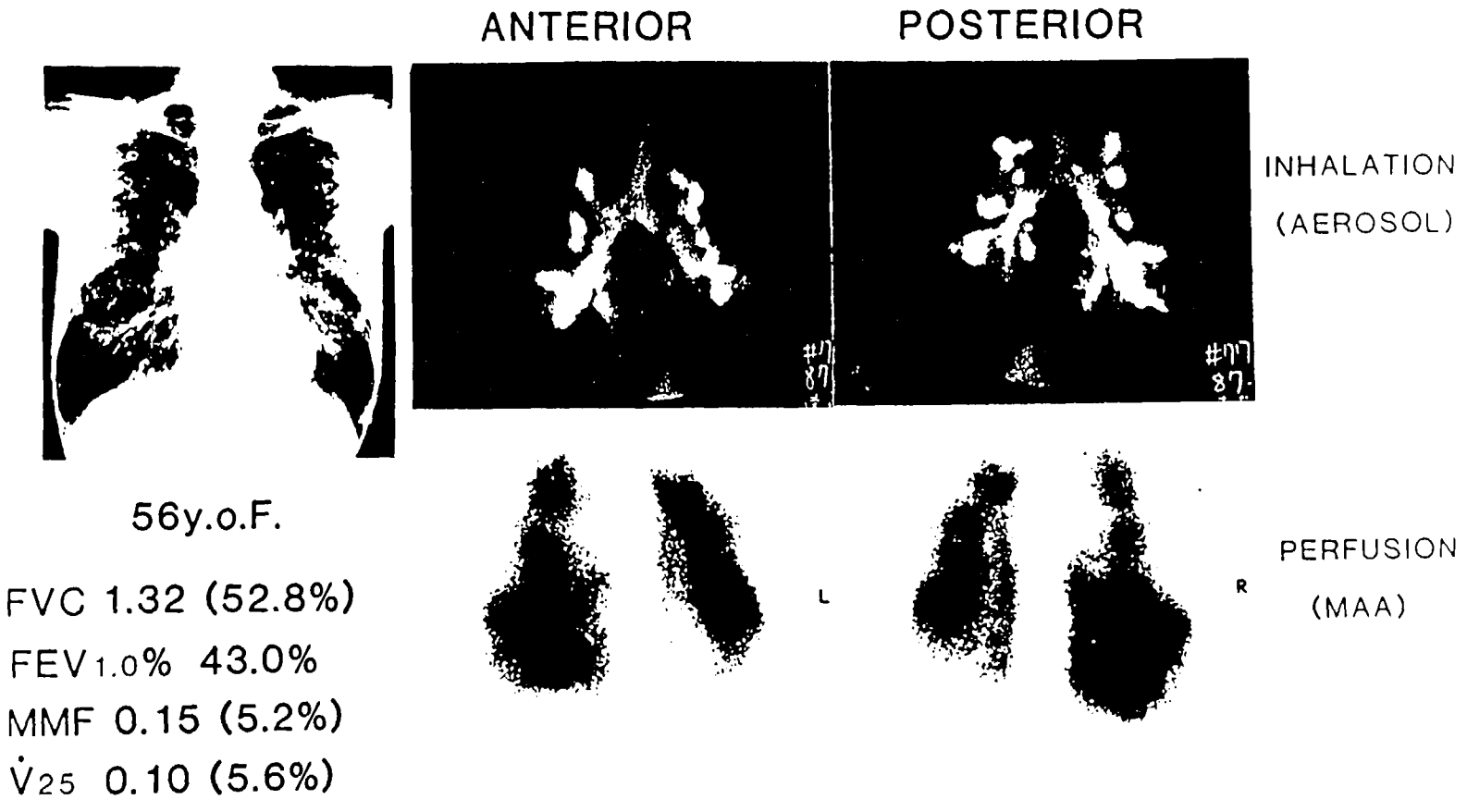



**Fig. 25.5** A 56 year old female with diffuse panbronchiolitis complaining of dyspnea for a long time. Diffuse panbronchiolitis is a diffuse lung disease of the transitional zone characterized by diffuse nodular densities, hyperinflation and hyperlucency on chest X-ray film and decreased vital capacity, forced expiratory volume and hypoxemia. Aerosol inhalation lung images indicate central deposition pattern as could be seen in emphysematous patients and perfusion is greatly diminished in lung regions where aerosol deposits less.

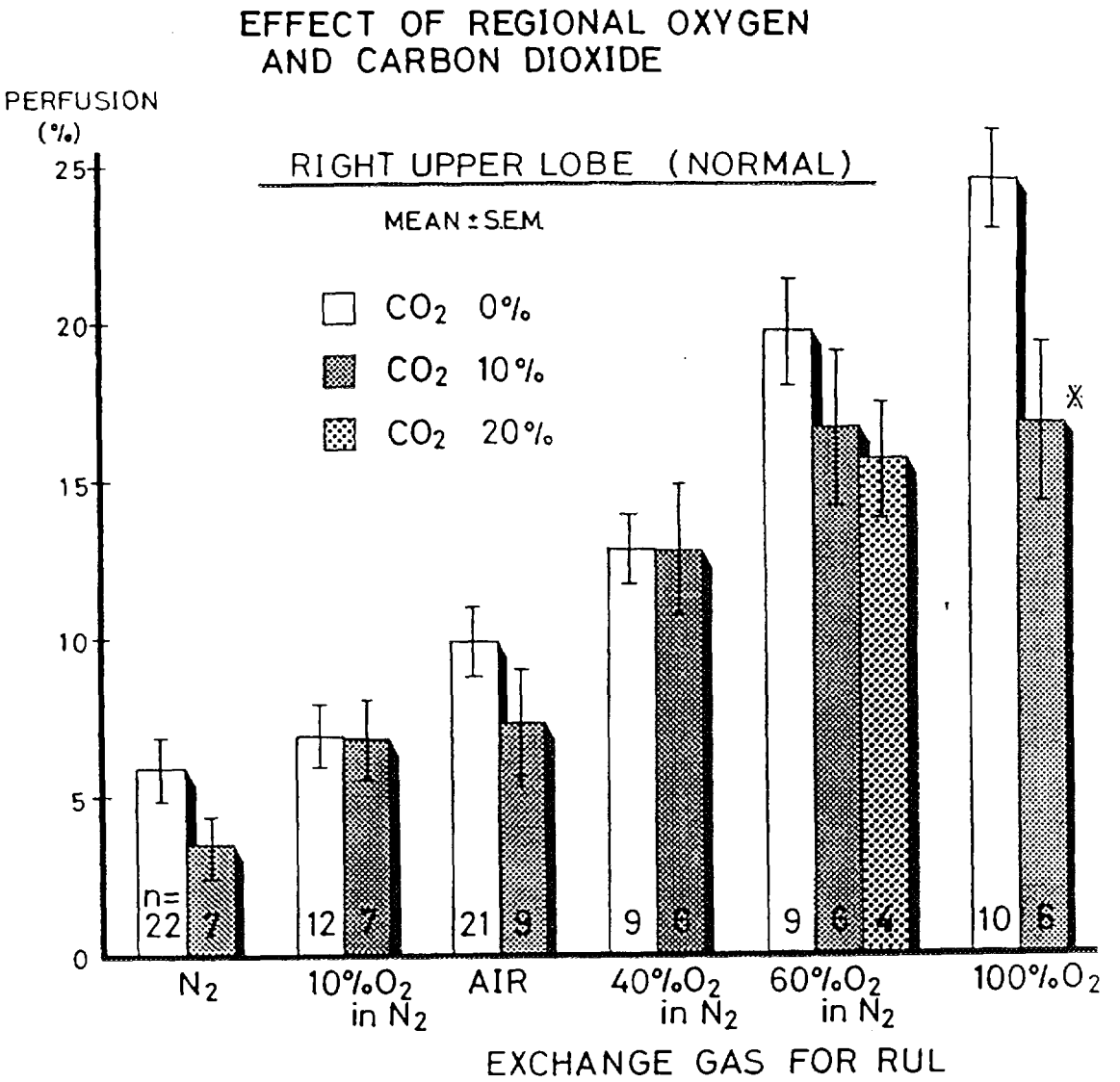



**Fig. 25.6** The right upper lobe of normal dog was artificially ventilated with gases of various oxygen concentrations. The regional perfusion distribution was diminished due to regional hypoxic vasoconstriction when the lobe was ventilated with gases of less oxygen tension than that of air. The regional perfusion distribution was increased because of vascular recruitment when it was ventilated with gases of higher oxygen tension than that of air.

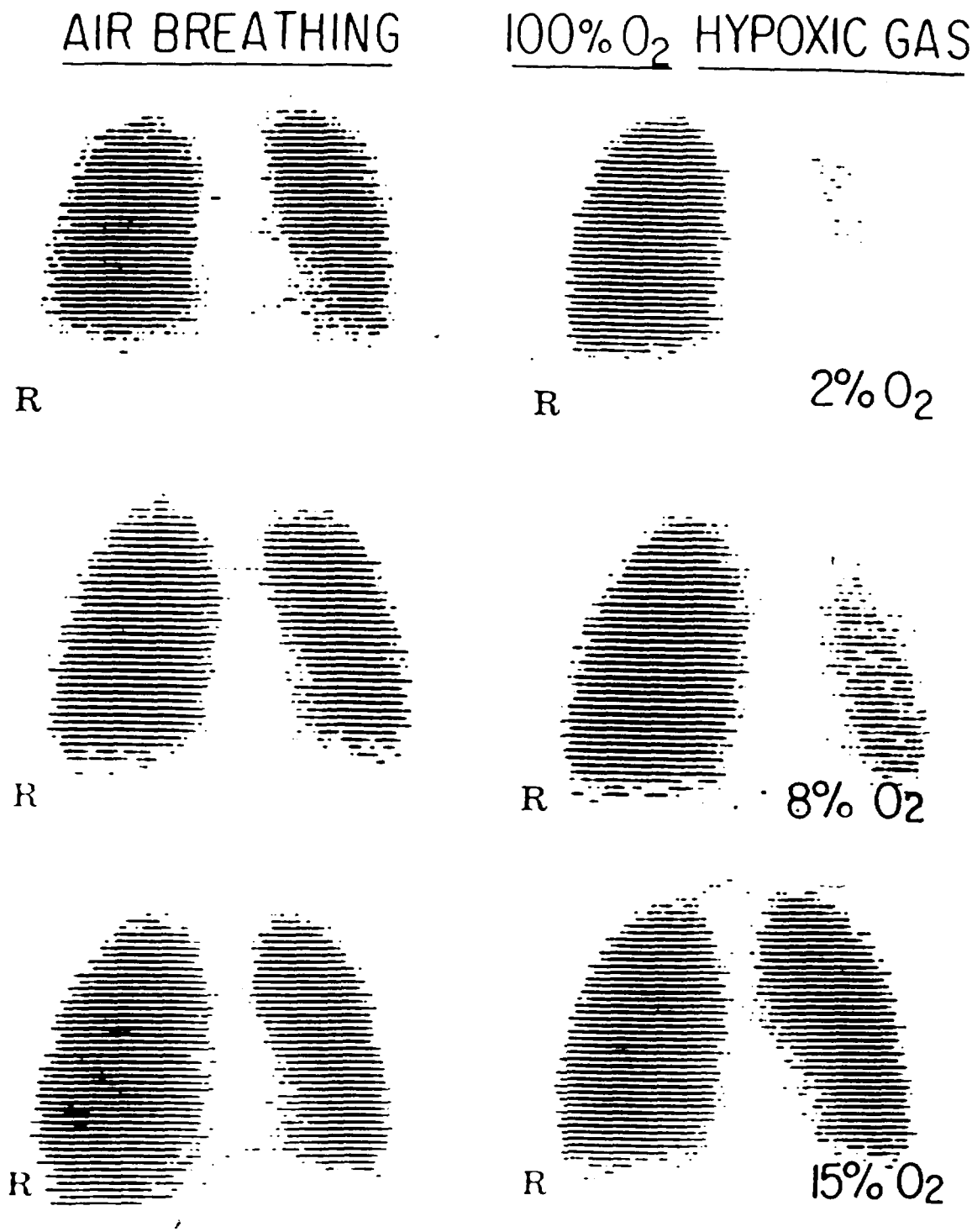



**Fig. 25.7** As compared with controls on the left hand side, perfusion in the left lung became diminished when the left lung was ventilated with hypoxic gases like 2%, 8% and 15% oxygen, while the right lung was ventilated with 100% oxygen.

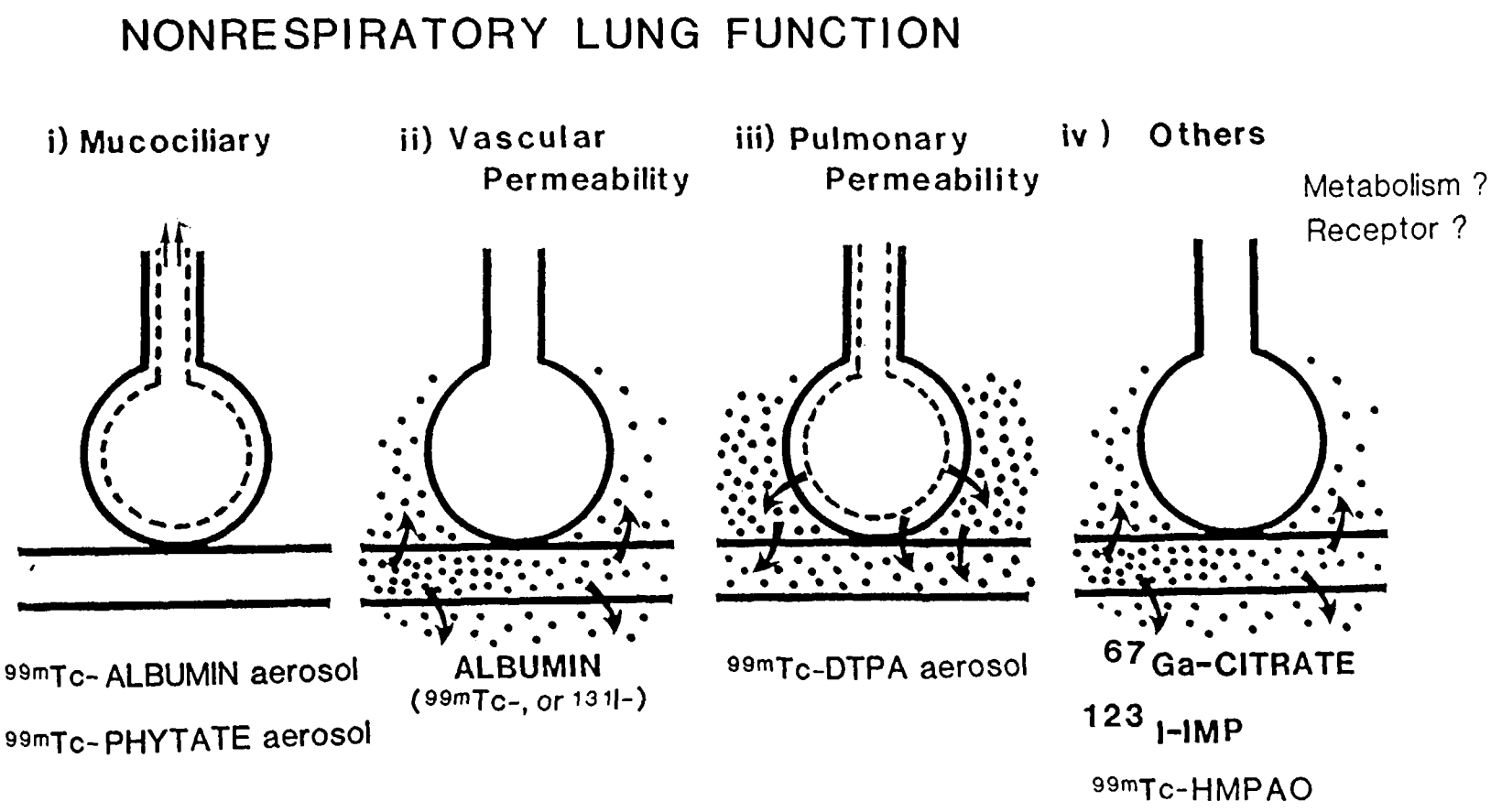
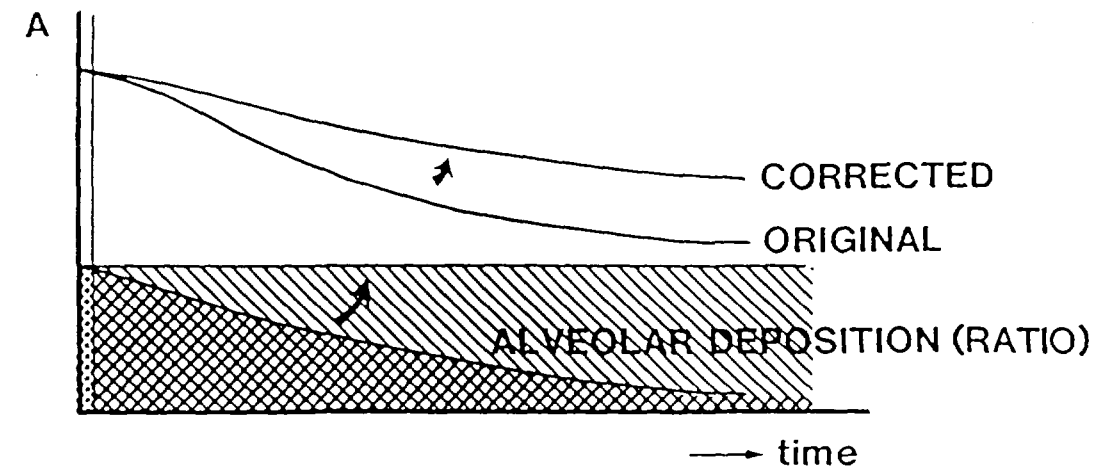
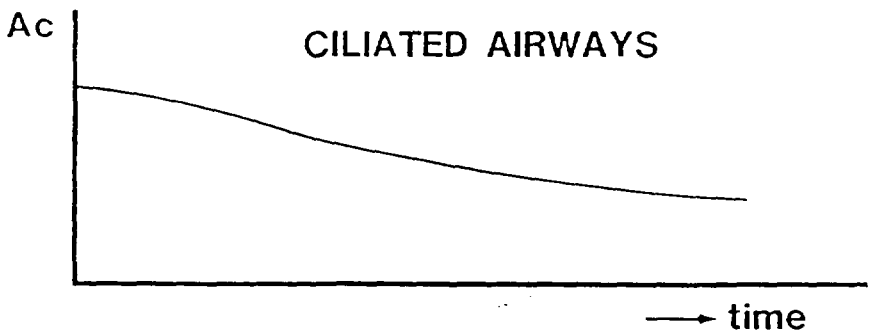



**Fig. 25.8** Schematic diagrams of various kinds of nonrespiratory lung function and radionuclides to study with.




: LUNG RETENTION RATIO




: AIRWAY RETENTION RATIO

: AIRWAY DEPOSITION RATIO

: AIRWAY CLEARANCE EFFICIENCY

**Fig. 25.9** Time activity curves constructed from sequential measurement of radioactivity. Alveolar deposition is the amount of radioactivity remaining in the lungs at 24 hours after body-background is subtracted. Lung retention ratio (LRR) is calculated from the corrected time activity curve. After the amount of alveolar deposition is subtracted, time activity curve only from the ciliated airways is constructed. Airway retention ratio (ARH), airway deposition ratio (ADR), airway clearance efficiency (ACR) are calculated.

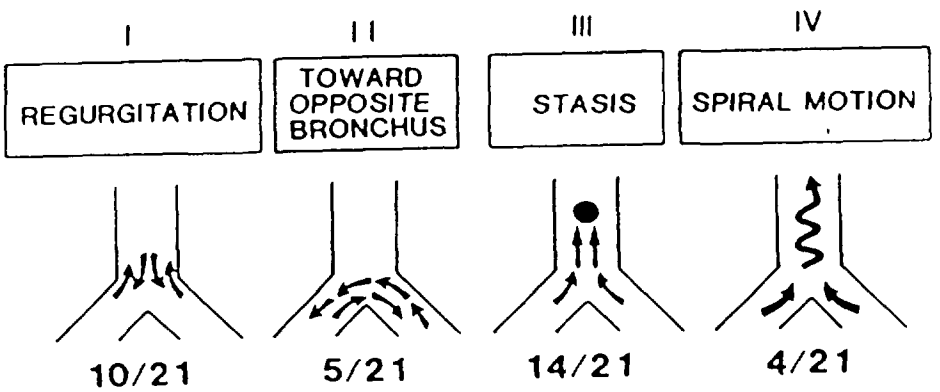



**Fig. 25.10** Four abnormal mucous transport patterns on the trachea. More or less similar patterns are seen on the ciliated airways. Numbers below the diagrams indicate approximate frequency in patients with COPD (18).

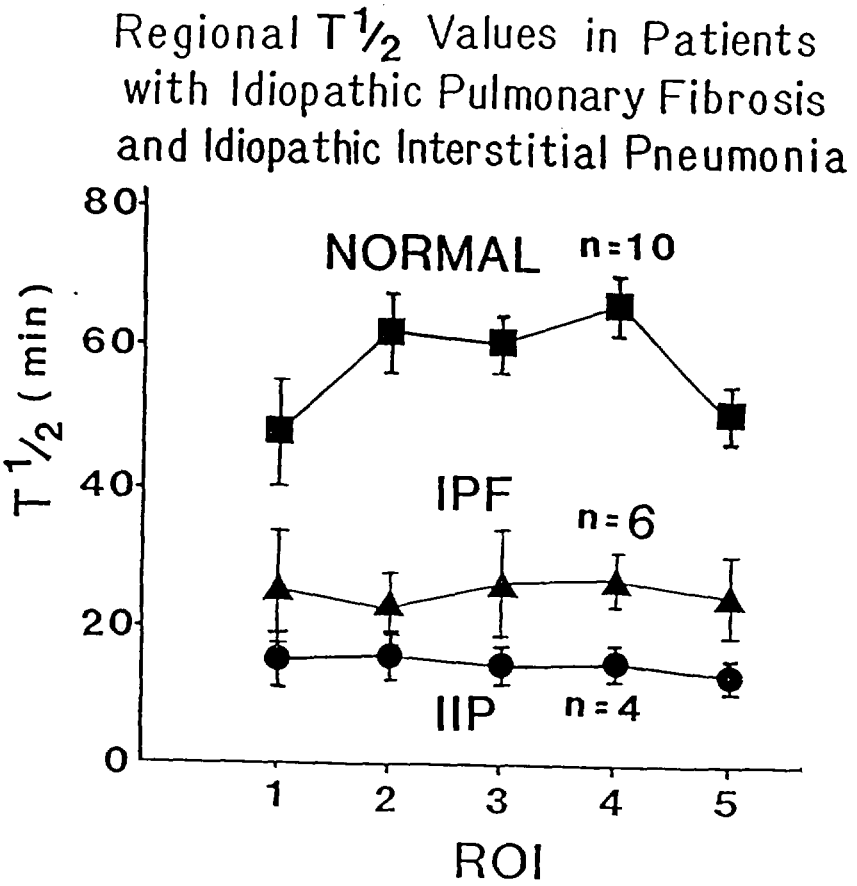



**Fig. 25.11** Half clearance time (T½) (mean ± S.E.) of ten normal subjects, six patients with idiopathic pulmonary fibrosis and four patients with idiopathic interstitial pneumonitis. T½ was measured at five different regions of interest (ROI). There was a statistically significant difference between them, indicating more permeable pulmonary epithelium in interstitial lung diseases. ROI 1: the left whole lung, ROI 2: the right whole lung, ROI 3: the upper third of the right lung, ROI 4: the middle third of the right lung and ROI 5: the lower third of the right lung parts of the lungs. In any lung regions (from one to six) T½ is smaller in the latter than the former.