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COMPARISON OF RADIOAEROSOL VERSUS RADIOXENON INHALATION PROCEDURES
IN OBSTRUCTIVE LUNG DISEASE AND PULMONARY EMBOLISM*

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INTRODUCTION

In the past five years, the application of lung perfusion scanning with macroaggregated albumin (MAA) as a test of regional lung perfusion has gained wide acceptance especially as an aid in the diagnosis of and management of pulmonary embolism (1-5). However, in recent years it has become apparent that perfusion defects even in the presence of normal chest x-ray findings are not always of vascular origin (6-8). In fact, among middle age and older patients underlying obstructive airway disease is a frequent cause of transient regional ischemia. Thus it is frequently important to be able to determine not only the patency of the pulmonary arteries but of the airways as well. For this reason alone, wider application of inhalation lung imaging procedures is urgently needed.

My objectives are to describe both the aerosol and the xenon gas procedures, their major uses, advantages, disadvantages and other differences. Table 1 compares radioaerosol versus 133 xenon gas lung imaging procedures regarding the functions measured, the abnormalities detectable and the indications for each of the two procedures. The radioaerosol scan is primarily a measure of airway patency and of muco-ciliary activity, whereas the xenon scan measures air flow dynamics and regional ventilation. The aerosol scan detects sites of partial and complete airway obstruction, and provides characteristic patterns of the pulmonary distribution of the aerosol. The xenon technique permits one to determine complete versus almost complete airway obstruction and identifies emphysematous lesions as slow spaces, for example, regions where gas can enter quite readily but where the gas is trapped and removed very slowly. The major indications of the aerosol procedure are in pulmonary embolism and obstructive airway diseases and as

TABLE 1

2

a substitute for bronchography. The xenon inhalation procedure is mainly indicated in obstructive lung disease, chronic emphysema and also in pulmonary embolism.

Current radioaerosol equipment and inhalation technique

For the past four years an ultrasonic nebulizer* is used in place of intermittent, positive gas pressure nebulizers. This device produces a more or highly concentrated aerosol and converts the test solution at a much faster rate (about 1 ml per minute versus 1 ml per 5-10 minutes). We usually use 5-8 ml of ^{99m}Tc albumin solution diluted with normal saline to bring the total volume to about 7 ml. This test dose is added to the nebulizer reservoir and the equipment is then ready for operation.

Routinely the patient is seated comfortably facing the nebulizer, which is located preferably in a negative pressure hood to prevent room contamination. The patient's nostrils are occluded by means of a nose clip. A practice inhalation procedure is performed using normal saline if the patient is apprehensive. Radioaerosol inhalation is started by requesting the patient to insert the mouthpiece which is connected with an uni-directional valve and by instructing him to breathe normally from the generator line. The exhaled air passes automatically through the exhaust line into the negative pressure hood. When all the solution has been nebulized (7-10 min) the mouthpiece and nose clip are removed and the patient is directed to rinse his mouth with water.

Lung imaging is begun immediately and the four standard views are obtained routinely. With available rapid imaging devices such as scintillation cameras, and multi-probe scanners, each view requires less than 5 min. A complete

*Mistogen Electronic Nebulizer, Mistogen Co., Oakland, Calif.

four-view examination can be done in less than one hour including the patient positioning and the 20 min required for the inhalation procedure.

Normal radioaerosol inhalation scans and postural effects

Chest scans obtained following radioaerosol inhalation in normal subjects usually show little or no radioactivity in the trachea and major bronchi. However, small amounts are occasionally found in the posterior pharynx and stomach. The normal lung images shown in Figure 1 provide objective evidence of airway patency to the aveoli. Such findings demonstrate that air flows freely to all parts of the lung.

← FIG. 1

Normally the apical regions show more radioactivity in the upright position than do perfusion scans because ventilation is less influenced by gravity than is perfusion. In the lateral decubitus positions, a larger amount of aerosol is deposited in the dependent lung but this is not a gravitational effect - it is related to increased ventilation of the inferior or dependent lung in these positions. See Figure 2.

← FIG. 2

Xenon inhalation technique

The xenon method which we have used is the standard single breath method in which the patient breathes in from residual volume to full vital capacity and is then instructed to hold his breath for 20-30 seconds during which period one generates a lung image with the scintillation camera. Subsequently, at 30 second intervals, while the patient is breathing room air, one follows the washout of the xenon gas. The gas is nearly completely removed by about 30-60 seconds and is entirely cleared from the lung within 2-3 minutes in normal subjects.

Bronchial patency and radioaerosol deposition

The author's concepts (9) regarding bronchial patency and the deposition

and retention of inhaled 0.5-3.0 μ size radioaerosols are presented diagrammatically in Figure 3. The trachea and major bronchi normally are not visualized by scanning because the amount of aerosol deposited there is far less than that retained in the lung parenchyma. The surface area of the major airways is infinitely small in comparison with the tennis court size of the alveolar surface. FIG. 3

With partial bronchial obstruction excessive deposition occurs on both sides of the constricted region as a result of turbulence, eddy currents, and impaction of the particles as they move more rapidly through the narrowed orifice during respiration. Discrete areas of highly concentrated radioactivity have been found at sites of proven obstruction in the major bronchi near the hilum in numerous patients with constrictive tuberculosis bronchial disease and in bronchogenic carcinoma. Similar but smaller foci of partial airway obstruction are found in patients with bronchitic emphysema and bronchiectasis.

When an airway is totally obstructed, the region beyond the site of occlusion shows no radioaerosol deposition, and there is no abnormal accumulation of radioactivity at the obstructed site. Furthermore, when the alveoli are filled with fluid or are collapsed, air cannot move in or out of the airways even though they are patent. Here the radioaerosol scans show an absence of radioactivity in the affected lung except for minimal amounts in the major airways.

It is the capability of the aerosol scan to disclose sites of partial airway obstruction or related airway disturbances by excessive regional aerosol deposition and retention. That is a characteristic feature of the aerosol method. An example of regional aerosol deposition at the site of

proved bronchial constriction is shown in Figure 4 wherein chest films and scan data are presented from a patient with bronchiectasis who had had a previous resection of the left lower lobe followed by constriction of the left upper lobe bronchus at the operative site. The entire left lung is not perfused and the site of the partial left upper lobe bronchus obstruction coincides with the hot spot or excessive aerosol deposition in this region.

← FIG. 4

Aerosol scans in chronic obstructive airway disease

In obstructive airway disease the aerosol scans are nearly always abnormal and show various deposition patterns (9-11). One major group of patients with findings characteristic of obstructive emphysema show perfusion and aerosol scan patterns which are nearly superimposeable (Figure 5). Some in this group have giant bullae but many show little or no radiographic evidence of regional bullous disease. In the "pure" emphysematous-type patient according to the classification of Burrows and Fletcher (12), the aerosol scans show excessive deposition of radioactivity in regions of the major airways (Figure 6) which are prone to collapse and become partially occluded during expiration as shown by Fraser (13) during cinebronchography. In the bronchitic-type patients according to the same classification, the aerosol patterns are distinctly different. Excessive aerosol deposition does not occur in the major airways but discrete regions of increased or reduced radioactivity are found in the more peripheral parts of the lung. In the inhalation and perfusion scans illustrated in Figure 7, particularly in the right lateral views, one sees a region which is neither ventilated nor perfused. Such a finding indicates complete airway obstruction and reduction of oxygen-tension in the alveoli to levels below 8 or 9 percent

← FIG. 5

← FIG. 6

← FIG. 7

which are known to produce reflex regional ischemia (14). Other areas in the right lateral view which show spotty excesses of aerosol deposition, indicate partial airway obstruction which is not associated with regional ischemia in the same areas. Presumably, the lack of associated ischemia indicates that the degree of obstruction was not sufficient to reduce regional oxygen concentration below 15 percent (14).

In nearly all types of chronic obstructive airway disease the aerosol inhalation scan patterns show far greater abnormalities than those observed in the perfusion scans (15). Such a relation is to be expected because in these patients the major physiological disturbance is obstruction of the large and/or small airways during expiration. The bronchitic-type patient is the one who is most likely to respond to anti-spasmodic and antibiotic treatment. The pure emphysema patient has much less chance of improvement unless surgical treatment is indicated for giant bullous disease. Unfortunately this situation is rare.

Aerosol vs xenon lung imaging in bronchogenic carcinoma

The following three composites which show the radiographic and lung imaging abnormalities in a patient with oat cell bronchogenic carcinoma are presented to illustrate certain differences between aerosol and xenon gas inhalation lung images before, during and after radiation therapy. In Figure 8a before treatment, the chest film demonstrates the left hilar lesion and the angiogram and anterior perfusion images disclose the nearly complete absence of perfusion to the entire left lung. The posterior view of the lung following aerosol inhalation shows a nearly complete absence of aerosol in the region of the left upper lobe. Also the trachea is abnormally visualized and excessive activity is deposited near the site of the bronchial lesion as

FIG. 8a

was found to obstruct the left upper lobe orifice at bronchoscopy. By comparison, posterior views of the chest following xenon inhalation show that both lung fields are nearly equally well ventilated and that the rate of washout is only slightly slower in the left upper lobe region. This is an example of how the radioaerosol inhalation scan exaggerates the degree of airway obstruction. In addition, the radiographic and scan results reveal two important features. First, the perfusion deficit in bronchitic carcinoma is usually due to pulmonary artery compression by either primary or metastatic tumor in the hilar region rather than being secondary to airway obstruction. Second, these findings are similar to those in pulmonary embolism where normal or near normal ventilation persists inspite of pulmonary arterial occlusion.

The composite presented in Figure 8b is from the same patient while FIG. 8b
undergoing radiation therapy. By this time the hilar mass has largely disappeared and a considerable improvement in perfusion to the left lung is now present. The aerosol scan provides evidence of almost complete obstruction of air flow to the left upper lung and also shows areas of excessive aerosol deposition in both hilar regions. By comparison, the xenon inhalation lung images show good ventilation to both lung fields including the left upper lobe. However, during washout some gas is trapped in the left upper lobe region. The latter findings demonstrate that gas can enter a lobe where the bronchos is nearly completely obstructed but the gas cannot be removed from this region as rapidly as from normal areas of the lung. Again, the aerosol scan exaggerates the degree of airway obstruction.

In the third composite (Figure 8c) the hilar lesion has continued to shrink and has been associated with further improvement in perfusion to the FIG. 8c

left lung. The aerosol scans show for the first time, distinct evidence of partial obstruction by a discrete region of excessive aerosol deposition at the tumor site in the left upper lobe bronchus. Although deposition in the trachea is no longer present, numerous areas of excessive aerosol retention persist throughout the lung as indicators of underlying generalized airway disease. On the other hand, the xenon gas inhalation lung images continue to show normal air flow throughout both lungs except in the washout phase when there is slight trapping of gas in the left upper lobe. These findings clearly demonstrate the differences in sensitivity between the aerosol and gas methods as indicators of partial airway obstruction. Although the aerosol scan exaggerates the degree of obstruction as in the left upper lobe bronchus, it also reveals evidence of generalized obstructive airway disease which is not shown by the radioxenon gas procedure.

Combined lung perfusion and inhalation imaging in suspected pulmonary embolism

During our past three years experience with lung perfusion and either radioaerosol or radioxenon inhalation imaging of patients with suspected pulmonary embolism, we have come to realize that a diagnosis of pulmonary embolism based on clinical findings, a normal chest film and a perfusion scan showing one or more areas of ischemia has a far lower probability of being correct than was originally believed. The main reason for the reduced significance of such findings is that obstructive airway disease which is frequently not revealed in the routine chest x-ray examination can still produce perfusion scan abnormalities indistinguishable from those found in pulmonary embolism. Underlying obstructive airways disease is frequently overlooked because many of these patients have long periods of remission without overt symptoms while others may well have become accustomed to their respiratory

disabilities of a chronic nature and do not volunteer such information to the physician. Certainly, the incidence of chronic bronchitis, bronchitic emphysema and other airway disorders is increasingly common among middle age and older patients. It is now our practice in suspected pulmonary embolism patients, to perform a radioaerosol inhalation scan whenever a history of pre-existing airway disease can be elicited. The additional information either strengthens the significance of the perfusion defects by showing that the ischemic regions are well ventilated or rules out the diagnosis of pulmonary embolism by providing evidence of underlying obstructive airway disease.

In the past two years all three types of lung imaging procedures have been performed with scintillation cameras following ^{99m}Tc MAA injection with the patient in the sitting position. When indicated, the radioaerosol inhalation procedure is performed after the patient has inhaled 5-10 mCi of ^{113m}In -dium-albumin aerosol. Both procedures can be performed at the same visit in most cases within 1-2 hours or less. When further information is needed regarding ventilatory dynamics, single breath xenon lung images are performed the next day.

The value of the combined perfusion-inhalation lung imaging studies are illustrated by the findings in two young women who were referred with diagnoses of suspected pulmonary embolism. In the first case, T.Q., an 18-year-old girl, perfusion scans are presented in Figure 9a, the 1st in November 1969, when she was first suspected of pulmonary embolism and again on the 13th of February when she returned to the hospital with a recurrence of her symptoms of shortness of breath and chest pain. On this admission her scan findings lead to a diagnosis of pulmonary embolism and she was treated with anti-coagulants (Figure 9b). She returned two weeks later, at which time a

FIG. 9a

history of asthma in childhood was elicited and aerosol inhalation scans were performed. It was demonstrated that her perfusion abnormalities were associated with underlying obstructive airway disease by the bronchitic type aerosol lung distribution patterns. She was then treated with antibiotics and bronchial dilator drugs following which she responded rapidly and upon reexamination by perfusion and aerosol inhalation scanning her previous blood flow and ventilatory disturbances were shown to have returned to normal (Figure 9c).

← FIG. 9c

Studies of the second illustrative case are presented in the next three composites. This 23 year-old young woman who was also on anti-pregnancy medication came to the hospital on May 19, 1970 with a history of sudden shortness of breath, nonproductive cough, and nonpleuritic substernal chest pain.

The negative chest x-ray findings and grossly abnormal perfusion scans in all four views with multiple perfusion deficits in both lung fields but mainly on the left are presented in Figure 10a. These perfusion scan findings are confirmed by the angiogram taken two days later. The second composite on this patient, shown in Figure 10b, demonstrates that the ischemic regions in the perfusion scan are well ventilated. Such findings strongly support the diagnosis of multiple pulmonary embolism. The third composite shows the results of a xenon gas ventilation study. Ventilation distribution and washout of xenon gas is perfectly normal in all respects. These findings likewise support the diagnosis of pulmonary embolism.

← FIG. 10a

← FIG. 10b

It should be noted that underlying obstructive airway disease cannot be excluded by normal pulmonary function test results. Neither can such disorders be ruled out by a normal single breath radioxenon lung imaging study.

What appears to be the most sensitive indicator of obstructive airway disease, is the radioaerosol inhalation scan. Some examples of this comparison have been shown in this presentation however work reported elsewhere by Isawa, Wasserman, and Taplin has amply demonstrated the relatively high sensitivity of the aerosol scan versus standard pulmonary function tests (16).

Comparison of lung inhalation imaging procedures

The radioaerosol and the radioxenon inhalation procedures each have definite advantages and disadvantages. With the radioaerosol method the advantages are: the procedure is performed with tidal volume respiration and relatively little patient cooperation is needed. Thereby, the great majority of patients, even those with severe respiratory disease can undergo this examination with practically no discomfort. The second advantage is that multiple views of the chest may be made following a single aerosol inhalation. Such a complete examination is possible because the distribution of the aerosol within the lungs remains relatively constant for several hours. A third assest is that the sites of partial and complete airway obstruction are detectable, as described previously. Furthermore, characteristic scan patterns of aerosol distribution are produced and thereby indicate the major types of obstructive airways disease. From a research viewpoint, the aerosol procedure also allows one to estimate muco-ciliary lung clearance rates and to detect regional disturbances of such mechanisms. Finally, a scanner as well as a camera may be employed.

The disadvantages of the aerosol method are first, air flow dynamics cannot be measured. Secondly, the procedure measures ventilation in normal or near normal subjects only. Third, it exaggerates the degree of airway obstruction in airway disease and finally there is extra pulmonary deposition

of radioactivity which may in some instances interfere with the interpretation of the lung images.

¹³³Xenon inhalation lung imaging

The advantages of the single breath inhalation and washout procedure is that it permits direct measurement of the distribution of ventilation both in patients with airway obstructive disease and in normal subjects. Probably the most important asset is that it allows one to measure (in quantitative fashion if desired) air flow dynamics, that is, the rates of gas entry and exit from various regions of the lung. Finally, repeated examinations may be made at frequent intervals because of the rapidity of gas exchange in the normal lung.

The disadvantages of the xenon method are first that only one projection or view of the lungs per examination can be made unless one desires to repeat the entire inhalation procedure with a second or third dose of radioxenon. Secondly, a camera is mandatory to generate lung images of xenon distribution at 20 second intervals or less. Third, breath holding is required of the patients for periods preferably as long as 20-30 seconds. This requirement eliminates many of the sick patients who could most benefit from the procedure. Another serious disadvantage is that the 80 kev gamma energy of ¹³³Xenon causes poor resolution of scan abnormalities and greatly decreases the sensitivity of the method to detect small lesions.

Radioaerosol method preferred in suspected pulmonary embolism

The reasons for this opinion of the senior author are: that the aerosol method requires minimal patient cooperation, diagnostic scan patterns are produced, breath holding is not required, and the site(s) of both partial and complete airway obstruction is visualized, multiple views of the chest may

be obtained following a single inhalation period, relatively small lung lesions are detectable as a result of optimum resolution of the images with the higher energy test agents and finally the lower costs of the special equipment and radionuclides used.

CONCLUSIONS

A normal perfusion scan excludes clinically significant pulmonary embolism and precludes the need for angiography. Scans showing loss of perfusion to an entire lung, a lobe, or a segment, together with a negative chest film, provide strong evidence for pulmonary embolism - angiography is nearly always confirmative but now seldom used. A normal aerosol scan rules out chronic and acute obstructive airway disease with equal or greater reliability than a normal perfusion scan excludes significant arterial occlusive disease. Perfusion and aerosol inhalation lung imaging should be performed in rapid sequence whenever underlying obstructive airway disease is suspected, because in such patients positive perfusion scans have much less diagnostic significance. The data from both perfusion and aerosol inhalation lung imaging permit an accurate diagnosis and appropriate treatment in all but the most complicated cases within 1-2 hours or less. Embolectomy is now rarely indicated.

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LEGENDS

- Figure 1 Aerosol inhalation scans in a normal volunteer performed with a Picker Dynapix - four minutes per view.
- Figure 2 Postural effects on aerosol inhalation scans of the left and right lateral decubitus positions during inhalation.
- Figure 3 Diagram of the author's concepts of radioaerosol air flow in and out of patent vs. partially and completely obstructed bronchi.
- Figure 4 Shows scan evidence of partial left upper lobe bronchus obstruction in a bronchiectatic patient by an area of excessive aerosol retention at the site of the proved partial obstruction.
- Figure 5 Shows the chest film and superimposable anterior perfusion and aerosol inhalation scans in bullous emphysema.
- Figure 6 Shows the chest film and perfusion and aerosol inhalation scans in a patient with "pure" pulmonary emphysema.
- Figure 7 Shows the inhalation and perfusion scan patterns in a patient with the bronchitic-type of emphysema. (See text for interpretation of lung images.)
- Figure 8a Shows the chest film, angiogram, perfusion scan, radioaerosol scan, and xenon images in a bronchogenic carcinoma patient prior to radiation therapy.
- Figure 8b Shows x-ray evidence of shrinkage of the left hilar lesion along with improvement in left lung perfusion. The aerosol scan indicates absence of ventilation to left upper lobe whereas the ¹³³Xenon lung images indicate only partial obstruction to this region.

Figure 8c Shows the same findings three weeks after completion of radiation therapy (6,000 r). At this time, perfusion of the left lung is further improved, the aerosol inhalation scan indicates continued obstruction in the left upper lobe bronchus as well as generalized obstruction disease whereas the xenon studies are normal other than for slight air trapping in the left upper lobe.

Figure 9a Shows perfusion scans in two views on two separate occasions in an 18-year-old girl suspected of pulmonary embolism. On the second examination multiple pulmonary ischemic regions are demonstrated.

Figure 9b Shows perfusion and aerosol inhalation scan patterns in the same patient 12 days later, wherein the ischemic regions are found to be nonventilated by the aerosol inhalation study and indicate a diagnosis of obstructive bronchitis.

Figure 9c Shows normal perfusion and aerosol inhalation lung images in the same patient approximately three weeks later following a course of antibiotics and anti-spasmodic therapy for her underlying bronchitis.

Figure 10a Shows a normal chest film and grossly abnormal perfusion lung images in a 23-year-old woman with suspected pulmonary embolism. The angiogram also shown here but taken two days later is confirmatory.

Figure 10b Shows four view perfusion and radioaerosol inhalation lung images made on the same day which demonstrate that the ischemic regions are well ventilated as in pulmonary embolism

Figure 10c Shows the gas inhalation lung images on the same patient made on the day after the combined perfusion-aerosol inhalation studies. The xenon lung images are normal in all respects.

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INHALATION LUNG IMAGING PROCEDURES

RADIOAEROSOL

¹³³XENON GAS

FUNCTIONS MEASURED

AIRWAY PATENCY
MUCOCILIARY ACTIVITY

AIR FLOW DYNAMICS
REGIONAL VENTILATION

DETECTABLE ABNORMALITIES

SITES OF PARTIAL AND
COMPLETE AIRWAY OBSTRUCTION
CHARACTERISTIC PATTERNS
OF PULMONARY DISTRIBUTION

COMPLETE vs. INCOMPLETE
AIRWAY OBSTRUCTION
IDENTIFIES BULLOUS LESIONS

MAJOR INDICATIONS

PULMONARY EMBOLISM
OBSTRUCTIVE AIRWAY DISEASES
SUBSTITUTE FOR BRONCHOGRAPHY

OBSTRUCTIVE LUNG DISEASES
EMPYSEMA, BULLOUS
PULMONARY EMBOLISM

AEROSOL INHALATION SCANS

A NORMAL VOLUNTEER

ANTERIOR

POSTERIOR

RIGHT LATERAL
C.B., ♂, 47

LEFT LATERAL

POSTERIOR INHALATION SCANS

SITTING

LEFT LATERAL DECUBITUS

RIGHT LATERAL DECUBITUS

AIR FLOW CODE

→ IN

← OUT

↓ DECREASED

↓↓ MINIMAL

○ NONE

ANTERIOR

PERFUSION

ANTERIOR

INHALATION

PERFUSION

INHALATION

PERFUSION

R

INHALATION

R

BRONCHITIC TYPE

J.T., ♂, 56

INHALATION

ANT.

POST.

RT. LAT.

PERFUSION

BRONCHOGENIC CARCINOMA - "OAT CELL"

M.H., ♀, 47 - 11/25/69

CHEST FILM

ARTERIOGRAM

ANT. PERFUSION IMAGE

^{99m}Tc -ALBUMIN
AEROSOL INHALATION

$^{133}\text{XENON}$ INHALATION

POSTERIOR VIEWS

BRONCHOGENIC CARCINOMA - "OAT CELL"

DURING RADIATION THERAPY (5000 R)

M.H., ♀, 47 - 1-28-70

PERFUSION IMAGES

^{99m}Tc -ALBUMIN
AEROSOL INHALATION

^{133}Xe XENON INHALATION

BRONCHOGENIC CARCINOMA - "OAT CELL"
 3 WEEKS AFTER COMPLETING RADIATION THERAPY (6000R)
 M.H., ♀, 47 - 2-20-70

PERFUSION IMAGES

^{113m}In -ALBUMIN
 AEROSOL INHALATION

$^{133}\text{XENON}$ INHALATION

PERFUSION SCANS

11-19-69

2-13-70

POSTERIOR VIEWS

LEFT LATERAL VIEWS

T.Q., ♀, 18

PERFUSION INHALATION

2-25-70

POSTERIOR VIEWS

LEFT LATERAL VIEWS

T.Q., ♀, 18

PERFUSION

INHALATION

3-12-70

POSTERIOR VIEWS

LEFT LATERAL VIEWS

T.Q., ♀, 18

5-19-70

5-21-70

ANTERIOR

POSTERIOR

RIGHT LATERAL

LEFT LATERAL

5-19-70

C.B., ♀, 23

PERFUSION SCANS (^{99m}Tc -MAA)

ANT.

POST.

RT. LAT.

L. LAT.

AEROSOL INHALATION SCANS (^{113m}In -ALB)

C.B., ♀, 23

5-19-70

^{133}Xe XENON GAS INHALATION SCANS (POSTERIOR VIEWS)

BREATH-HOLD
10 SEC

WASH-OUT
0 - 30 SEC

WASH-OUT
60 - 90 SEC

WASH-OUT
150 - 180 SEC

C.B., ♀, 23

5-20-70