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COMPARISON OF THREE RADIOPHARMACEUTICALS FOR LUNG VENTILATION IMAGING

Dr Osayande Evbuomwan

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Declaration

I, Dr Evbuomwan Osayande declare that this research report is my own, unaided work. It is being submitted for the degree of Master of Medicine (Mmed) at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

(Signature of candidate)

28th day of May 2018 in Johannesburg.

Master of Medicine in the branch of Nuclear Medicine

My wife and daughter: Thank you for giving me the opportunity and atmosphere to further my academic career. Thank you for the support and prayers. I love you both.

My parents: Thank you for your support with my studies all through these years. Without you both I would not be here today. I am forever grateful.

Abstract

A variety of radioaerosols have been tested in the past for lung ventilation scintigraphy in the assessment of pulmonary thromboembolism. Amongst these are the bone scan agent technetium 99m (^{99m}Tc) methylene diphosphonate (MDP) and the myocardial perfusion agent ^{99m}Tc methoxy isobutyl isonitrile (MIBI). However, ^{99m}Tc diethylenetriaminepentaacetic acid (DTPA) currently remains the most commonly utilized agent.

The aim of this study was to compare the image quality and alveolar clearance of MDP, DTPA and MIBI as ventilating agents in patients being investigated for pulmonary thromboembolism.

Patients referred to our institution from August 2015 to July 2017 for a ventilation – perfusion (VQ) scan, who fulfilled the inclusion criteria were enrolled into the study as participants. Each ventilation agent was used to ventilate 43 participants, making a total of 129 participants in the study. Images were assessed for quality and alveolar clearance qualitatively and semi-quantitatively respectively by a nuclear medicine physician blinded to the agent used.

^{99m}Tc MIBI had superior image quality and slower alveolar clearance, with statistically very significant different results when compared to ^{99m}Tc DTPA.

Acknowledgements

- A big thank you to the staff of the Nuclear Medicine Department at Charlotte Maxeke Johannesburg Academic Hospital for the practical implementation of this study.
- A special thanks to Mr. Desmond Malema and the radiographers for their support and understanding.
- I would also like to acknowledge and extend my gratitude to my supervisor and mentor, Professor Vangu and my co supervisor Dr Purbhoo for their continued support.

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Nomenclature/List of Abbreviations and Symbols (in order of appearance)

1. ^{99m}Tc - Technetium 99 Metastable
2. MDP - Methylene Diphosphonate
3. MIBI - Methoxy Isobutyl Isonitrile
4. DTPA – Diethylene Triamine Pentaacetic Acid
5. VQ – Ventilation Perfusion
6. PTE – Pulmonary Thrombo Embolism
7. ^{133}Xe – Xenon 133
8. ^{81m}Kr – Krypton 81 Metastable
9. ^{81}Rb – Rubidium 81
10. SPECT - Single Photon Emission Computed Tomography
11. FDA - Food and Drug Administration
12. HDP – Hydroxy methylene Diphosphonate
13. ^{99m} TcO4 - Technetium 99 Metastable Pertechnetate
14. ^{99m}Tc-Sn-Phytate - Technetium 99 Metastable Stannous Phytate
15. ^{111}In-Cl_3 - Indium 111 Chloride
16. ^{111}In DTPA - Indium 111 Diethylene Triamine Pentaacetic Acid
17. PYP – Pyrophosphate
18. MAA - Macroaggregated Albumin
19. ROI - Region of Interest
20. ANOVA – Analysis of Variance

CHAPTER 1 - INTRODUCTION

1.1 Rationale

The big question is, can Technetium 99 metastable methylene diphosphonate (^{99m}Tc-MDP) and ^{99m}Tc methoxy isobutyl isonitrile (^{99m}Tc- MIBI) effectively replace ^{99m}Tc diethylene triamine pentaacetic acid (^{99m}Tc-DTPA) as radioaerosols for lung ventilation scintigraphy in a busy nuclear medicine facility that routinely uses MDP and/or MIBI on a daily basis?

Numerous radiopharmaceuticals in the form of radioaerosols have been used/tested for ventilation scintigraphy, including ^{99m}Tc-MDP and ^{99m}Tc- MIBI. It is well known that the recommended radioaerosol for ventilation scintigraphy is ^{99m}Tc diethylene triamine pentaacetic acid (^{99m}Tc-DTPA). However, opening one vial per patient is not economically ideal, particularly in resource constrained regions. Studies have also shown the disadvantages of using ^{99m}Tc-DTPA for ventilation scintigraphy.

Both MDP and MIBI are available daily in our department, as they are used for other investigations like bone scanning and myocardial perfusion imaging (MPI), therefore spare doses would always be available. We assessed if these agents could be used as alternatives to ^{99m}Tc-DTPA in our busy nuclear medicine department. The direct consequences of the possible outcome will be cost saving to the department and the hospital.

1.2 Background

Lung scintigraphy is a diagnostic imaging procedure that uses perfusion and/or ventilation scintigraphy to evaluate pulmonary and cardiovascular disorders.(1) It is one of the frequent investigations carried out in a nuclear medicine department. The most common clinical indication is to determine the likelihood of pulmonary thromboembolism (PTE).(1) The ventilation scan maps regional ventilation and helps define lung borders, thereby assisting in the recognition of peripheral perfusion defects.(2)

Various classes of agents are available for ventilation scintigraphy. These include gases, nanoparticles and aerosols. Currently, most nuclear medicine centers use radioaerosols for lung ventilation scintigraphy due to its availability, low cost technology and ease of operation.(3)

Aerosol ventilation scintigraphy is a diagnostic test that records the bronchopulmonary distribution of inhaled radioaerosols within the lungs.(1) An aerosol is a relatively time stable two phase system consisting of particles suspended in air or gas.(2) They can be produced by numerous nebulizers available in the market today.

Over time, different methods have been developed for the delivery of radiotracers into the lungs. Initially, work was centered on the use of gases like Xenon 133 (^{133}Xe) and Krypton 81 metastable (^{81m}Kr).(4) Ventilation imaging was performed for the first time with ^{133}Xe in 1969.(5) However, there are disadvantages in using either of these gases. ^{133}Xe has low energy and thus gives poor resolution images. It also has a very short biological half-life, allowing only posterior images to be acquired. As for ^{81m}Kr, it is produced from a Rubidium 81 (^{81}Rb) generator, which is in turn produced from a cyclotron and the cost of production makes it unavailable in most nuclear medicine departments.(6) These disadvantages have led to the use of radioaerosols as the main agents for lung ventilation scintigraphy today.

As far back as in the early eighties, it was believed that majority of nuclear medicine departments started using radioaerosols as the primary ventilation agent due to the disadvantages of the gases.(7) This is not to say that even in the late sixties, Taplin et al had already proposed radioaerosols for the study of lung ventilation.(8, 9)

The first radiopharmaceutical used for radioaerosol studies was Human serum albumin or its derivatives.(10) Since then several other tracers including DTPA, pyrophosphates and various

colloids have been investigated.(10, 11) Interestingly, pyrophosphates and colloids resulted in higher quality images (12), but DTPA was the radiopharmaceutical widely adopted.(10)

In 1978, Taplin and his team proposed using ^{99m}Tc-DTPA aerosol as a replacement for ^{133}Xe and this is believed to have given rise to the popular use of ^{99m}Tc-DTPA radioaerosol as a ventilation agent.(13) Since then several reports using DTPA for lung ventilation imaging have been published.(14) It is also postulated that ^{99m}Tc-DTPA gained popularity as the widely used radioaerosol today because of the reasons that follow. It was previously used for the measurement of lung permeability(6) and nebulizer manufacturers used ^{99m}Tc-DTPA in their clinical trials, which was then recommended in their package insert.(10)

An ideal radioaerosol should be readily available, cheap, produce good quality lung images, easy to use and non-toxic.(15) We are also in the era of single photon emission computed tomography (SPECT) ventilation and perfusion imaging.(16) This means that a good radioaerosol for SPECT ventilation lung imaging must have some additional characteristics. They should possess minimal major airway adherence, high alveolar deposition, slow clearance from the lungs and acceptable radiation absorbed dose.(11) Slow clearance from the lungs is the most important characteristic for obvious reasons. However, DTPA has rapid alveolar clearance, which can limit its use in SPECT lung imaging.(11) A more rapid washout is also known to occur in patients with inflammatory lung disease.(10) It is also postulated that there is an increase in lung clearance of DTPA in embolized regions.(12)

Even though DTPA is the food and drug administration (FDA) approved tracer for lung ventilation imaging,(3) some centers use other radiopharmaceuticals as their preferred radioaerosols due to the disadvantages that DTPA possesses and their availability. For example, at the university of Iowa, lung ventilation imaging has been done with ^{99m}Tc-sulfur colloid since 2000.(10)

It is worth mentioning that Technegas, an ultrafine aerosol of ^{99m}Tc labelled carbon, was developed with qualities superior to DTPA and other radiopharmaceuticals used as radioaerosols for lung ventilation imaging.(15) However, this technique is more expensive and technically demanding.(3)

Looking at the history of radioaerosols it can be said that DTPA does not tick all the boxes of an ideal radioaerosol for lung ventilation imaging in the assessment of PTE currently. Since drugs (including radiopharmaceuticals) used intravenously are also eligible for inhalation route,(17) other readily available radiopharmaceuticals used intravenously can be tried as lung ventilation agents.

^{99m}Tc MDP and ^{99m}Tc MIBI are used daily in our department and spare doses are readily available. Very few studies have looked at these agents as radioaerosols for lung ventilation imaging and some have shown superiority of these agents over DTPA.(3, 11, 18, 19) Therefore, we have decided to see if these agents can be routinely used in our department for lung ventilation imaging, as this would prove to be cost effective in the long run.

1.3 Study objectives

The main aim of our study was to compare ^{99m}Tc MDP, ^{99m}Tc MIBI and ^{99m}Tc DTPA as lung ventilation agents in the assessment of patients with suspected PTE. Considering the disadvantages of DTPA, the alternatives, MDP and MIBI, might be better and cost-effective alternatives for this study in our busy nuclear medicine facility. The objectives include;

- To compare the image quality of the three radiopharmaceuticals in participants being investigated for PTE.re
- To compare the alveolar clearance time of these three radiopharmaceuticals.

1.4 Literature review

To the best of our knowledge and after a thorough literature search, there are no randomized prospective studies comparing ^{99m}Tc-MDP and/or ^{99m}Tc-MIBI with ^{99m}Tc-DTPA for lung ventilation scintigraphy.

Many studies have explored the use of various radioaerosols for lung ventilation imaging in the assessment of PE. Most of these studies are old, as far back as the early 60s.(11) They have looked at the image quality of various radioaerosols as well as the alveolar clearance. Some of these radioaerosols have also been compared with ^{99m}Tc-DTPA. These radioaerosols have been tried out by various investigators all in a bid of identifying the ideal agent or getting suitable substitutes to DTPA in centers were DTPA is not readily available due to sporadic interruptions in supply.

Some of the most recent studies include a case report in 2017 by Colin and Kalpna.(19) They demonstrated that ^{99m}Tc hydroxy methylene diphosphonate (HDP), a radiopharmaceutical used in bone scintigraphy, like MDP, was a safe, reliable and cheaper alternative to ^{99m}Tc DTPA as a radioaerosol in the assessment of patients with suspected pulmonary embolism. Being a case report with just two patients a valid conclusion cannot be drawn. Although previous research has shown that ^{99m}Tc phosphate compounds including diphosphonates have high alveoli deposition and slower alveoli clearance rates and thus provide suitable aerosols for pulmonary ventilation studies.(11)

In one of the series we came across, ^{99m}Tc MIBI was directly compared to ^{99m}Tc DTPA as radioaerosols for lung ventilation imaging. This was carried out with the hypothesis that lipophilic cations like MIBI may be more suitable for ventilation lung scintigraphy. One of the findings in that series was lipophilic compounds such as ^{99m}Tc MIBI had slower alveolar clearance and superior imaging quality when compared to ^{99m}Tc DTPA.(3)

More earlier studies looking at various radioaerosols include the study in 1974 by Isitman et al.(20) In that series, they compared alveolar deposition and pulmonary clearance of ^{99m}Tc pertechnetate (^{99m} TcO4), ^{99m}Tc stannous phytate (^{99m}Tc-Sn-Phytate), Indium 111 chloride (^{111}In-Cl_3) and ^{111}In DTPA in 12 volunteers. They concluded that ^{99m}Tc-Sn-Phytate showed excellent alveolar deposition, slower clearance rate and slight accumulation in the tracheobronchial tree, as compared to the other agents. Again ^{99m}Tc-Sn-Phytate was investigated 20 years later by Peltier et al.(21), when they compared it with Technegas in 50 patients. They concluded that the image quality of Technegas was superior in most cases, but that interpretation of the lung ventilation study was comparable with both tracers.

Isitman and colleagues (11) also compared ^{99m}Tc Pyrophosphate (PYP) and ^{99m}Tc-DTPA as radioaerosols for SPECT ventilation lung imaging in 8 non-smoking volunteers. They concluded that ^{99m}Tc phosphate compounds like pyrophosphate had better alveolar deposition and slower clearance rates. Peltier and Chatal also had similar findings when they compared ^{99m}Tc DTPA with ^{99m}Te-rhenium in 77 patients with suspected PTE.(12)

Many radiopharmaceuticals have been investigated in the past as radioaerosols for lung ventilation imaging. This is most likely because researchers were looking for the ideal radioaerosol that will tick all the boxes. With the everyday availability of MIBI and MDP in our facility, we have decided to conduct a prospective randomized study, comparing them with DTPA as radioaerosols for lung ventilation imaging in patients with suspected pulmonary embolism.

CHAPTER 2 - MATERIALS AND METHODS

Ethics approval was obtained from the University of Witwatersrand's Human Research Ethics Committee (HREC), with ethics clearance number M150732.

2.1 Study design

The study was a randomized prospective cross-sectional study.

2.2 Study population

One hundred and twenty-nine participants referred for ventilation scintigraphy as part of the diagnostic investigation for suspected PTE and who met the inclusion criteria (Table 1) were prospectively studied. This made a total of 43 patients in each group of ventilation agent. Recruitment period was between August 2015 and August 2017. Signed consent was obtained from all study participants.

2.3 Randomization

A computer generated randomized system was used to select participants to be ventilated with any of the three agents. Forty-three patients each were randomized into the DTPA, MDP and MIBI groups.

2.4 Equipment

Each study participant was ventilated with the SmartVent™ (Diagnostic Imaging Limited UK) radioaerosol delivery system. This device uses an electronic micropump to produce aerosols from liquids, with a volumetric mean diameter of 1.32 microns. It is breath activated and gives on demand aerosol delivery.

Images were acquired using the GE Infinia Hawkeye GP3 (2006, WI, USA) camera and the GE Optima 649 (2014, WI, USA) gamma camera. Both cameras are double headed, with similar work stations and processing units.

Table 2.1 Inclusion and exclusion criteria

Inclusion criteria	**Exclusion criteria**
• All adult participants with a normal recent (<24 hours) chest x-ray (no consolidation or pleural effusion) • All non-smokers and healthy smokers able to ventilate adequately (count rate of 500 counts/secs or more)	• Debilitated participants who are not able to ventilate properly • Participants who will be ventilated with other ventilation delivery system other than the SmartVent radioaerosol delivery system • Participants with abnormal recent (<24 hours) chest x-rays

2.5 Ventilation procedure

Each of the study participants were ventilated with the SmartVent™ radioaerosol delivery system using the manufacturers' protocol. The generator chamber of the radioaerosol delivery system was loaded with approximately 25mCi of radiotracer in 1 ml (^{99m}Tc DTPA, ^{99m}Tc MIBI or ^{99m}Tc MDP) per subject. Each participant was positioned in the erect position (sitting) with a nose clip. With the tubing erect, they were told to suck and blow on the mouth piece like a straw for a few seconds before pressing the start button to commence ventilation. Each participant ventilated for about 90 seconds, to get a flow rate of about 0.6 mls/min. After all the radioaerosol had been delivered, each participant continued to breathe for about 20 seconds with the tubing in the mouth before taking off the nose clip.

2.6 Acquisition protocol

A large field of view gamma camera equipped with a low energy high resolution (LEHR) collimator was used. Acquisition occurred for all participants within 5 minutes of completing ventilation. The usual ventilation scanning protocol was used, with little modification. Each participant was imaged in the supine position, starting with an anterior/posterior static acquisition for 5 minutes (300 seconds). Every other view (lateral and posterior oblique images) was acquired for 3 minutes (180 seconds) each. At the end of the last view, participants remained supine for 10 minutes, and then a repeat anterior/posterior view was acquired for 3 minutes (180 seconds) before injection of macroaggregated albumin (MAA) to commence the perfusion study.

2.7 Image processing

Images were processed using the Xeleris work stations for both gamma cameras. The initial and later anterior and posterior images of the lungs were qualitatively assessed for regional, central and stomach distribution and semi quantitatively assessed for radioaerosol retention. Semi quantitative assessment was achieved by tracing a region of interest (ROI) around the periphery of both lungs on the early and late posterior images (Figure 1). The ROI drawn for the first set of images was directly copied onto the second set of images to increase reproducibility. The counts in each lung field were noted and summed up to get total number of counts in both lungs. The

count rate of the early images was also noted.

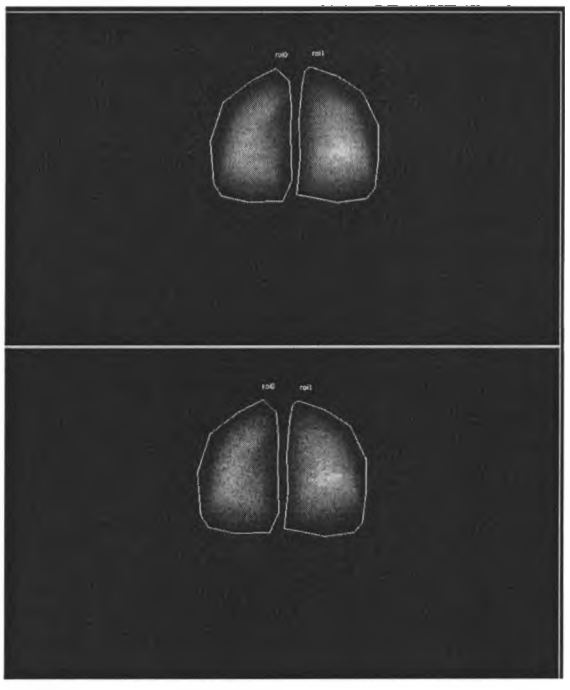

Figure 2.1 Early (top) and late (bottom) posterior images of the lungs demonstrating how the areas of interest were drawn

2.8 Data analysis

Data from each study participant was collected using Microsoft excel 2016, and was analyzed using the statistical package STATA. An experienced nuclear medicine physician evaluated the raw data of both the early and late posterior images of the lungs. The physician was blinded to which radioaerosol was used for the study being evaluated.

Visual (qualitative) assessment of the early and late posterior images to derive scores based on the quality of the image (peripheral penetration and central/stomach deposition) was used. This scoring system was a slight modification of the system used by NJ Carter.(4)

The scoring was as follows;

4 – no central deposition, good peripheral penetration

3 – central deposition but good peripheral penetration

2 – central deposition, poor peripheral penetration

1 – not interpretable

For the semi-quantitative assessment, a region of interest was manually drawn on the early posterior images taking the isocontour at 10% of maximum pixel of both fields and then copied and pasted on the delayed posterior images. This was a modification of the method used by Patrick P.(21) The counts of each ROI were recorded and the count rate of the initial 5minute image was noted.

2.9 Statistical analysis

Data were analyzed using STATA 13.1 package, MP – parallel edition (StataCorp LP, Texas, USA).

The results of the following variables; sex, smoking status, scan outcome and camera used were presented as frequencies and percentages. Age was represented as the mean and standard deviation.

Analysis of variance (ANOVA), with Bonferroni correction was used to analyze the differences between group means for the following;

- count rate
- initial counts
- alveolar clearance.

ANOVA alone was used to compare the following means;

- doses of radioaerosol used
- time interval between ventilation and initial acquisition
- time interval between the initial and later anterior/posterior acquisitions

Logistic regression was used for analysis and comparison between groups for the following categorical variables;

- Trachea and bronchi activity
- Stomach activity
- Image quality

Statistical significance was set as $p< 0.05$.

CHAPTER 3 - RESULTS

Overall, the study was well tolerated. None of the study participants presented with an irritating cough, bronchospasm or any other side effects.

Sixty-five participants were scanned using the GE Infinia camera, while the other 64 were scanned with the use of GE Optima camera. Characteristics of the study group are shown in table 2.

The mean dose of radioaerosol administered was 24.75mCi, with a minimum and maximum dose of 20 and 26mCi respectively. There was no statistically significant difference between the doses used for the three radioaerosols ($p= 0.8101$).

The mean time interval between ventilation and scan acquisition was 4.77 minutes, with a minimum and maximum time of 4 and 6 minutes respectively. This was not statistically significantly different between the three groups ($p= 0.4004$).

Participants had a mean time interval between the early and late anterior/posterior acquisition of 22.37 minutes, with a minimum and maximum time of 20 and 25 minutes respectively. This was also not statistically significantly different between the three groups ($p= 0.3932$).

Looking at the mean count rates of the three radioaerosols on the early 5 minutes posterior acquisition, MIBI had higher count rates when compared to DTPA and MDP, with a statistically significant difference when compared to DTPA ($p=0.021$). This is shown in table 3. We did not find any statistically significant difference between the count rates in smokers/previous smokers and subjects who had never smoked ($p=0.4439$)

All subjects had their early anterior/posterior images acquired for 5 minutes and the total initial counts on the posterior images for all subjects was assessed (table 4).

Alveolar clearance of the three radioaerosols was compared using ANOVA, with Bonferroni correction as shown in table 5. MIBI clearly showed a very significant slow alveolar clearance when compared to DTPA ($p = <0.0001$) and MDP ($p = < 0.001$). However, even though the mean alveolar clearance of all the subjects was 51%, they were 5 subjects that had extremely low alveolar clearance and this was not tracer dependent. Two patients in the MIBI group had alveolar clearance of just 14 % and 16%, a non-smoker and a previous smoker respectively. One patient in the DTPA group, a non-smoker had alveolar clearance of just 16%. While two patients in the MDP group had alveolar clearance of 21 % and 24%, a previous smoker and non-smoker respectively. In general, there was no statistical significant difference between the alveolar clearance in smokers and previous smokers versus subjects who had never smoked ($p=0.1252$)

In terms of image quality, none of the 129 participants had non-interpretable images or images with poor peripheral penetration. MIBI generally had better quality images as compared to the other two radioaerosols, with a statistically significant difference when compared with DTPA ($p= 0.001$) [table 6]. The MIBI group had the least number of participants with bronchial and/or tracheal activity, with a statistically significant difference when compared to the DTPA group ($p=0.004$). There was also a statistically significant difference between MIBI and DTPA in terms of stomach activity, with MIBI having less participants with stomach activity ($p=0.04$)

Table 3.1 Characteristics of the study group

Age(n=129) study	
Mean(SD)	47(±17 years)
Range	20-88 years
Sex(n=129) [a]	
Female	83(64)
Male	46(36)
Smoking status(n=129) [a]	
Never	95(74)
Previous	20(15)
Active	14(11)
Outcome [a]	
PE Absent	114(88)
PE present	14(11)
Non-diagnostic	1(1)

[a]: Values are represented as frequencies, and as percentages in parenthesis. SD – standard deviation. PE – pulmonary embolism

Table 3.2 Mean count rates of the three radioaerosols

TRACER	MEAN(c/s)	SD	FREQUENCY	P-VALUE
DTPA	957	346	43	
MDP	1164	520	43	
MIBI	1241	546	43	**0.0201**
TOTAL	**1121**	**490**	**129**	
DTPA	957	346	43	0.142
MDP	1164	520	43	
MDP	1164	520	43	1.00
MIBI	1241	546	43	
DTPA	957	346	43	**0.021**
MIBI	1241	546	43	

ANOVA was used for analysis and Bonferroni was used for correction between each group. c/s – counts per seconds, SD – standard deviation

Table 3.3 Summary of initial counts

TRACER	MEAN ©	SD	FREQUENCY	P-VALUE
DTPA	216813	85616	43	
MDP	267814	129653	43	
MIBI	285268	140245	43	**0.0268**
TOTAL	**256632**	**123389**	**129**	
DTPA	216813	85616	43	0.158
MDP	267814	129653	43	
MDP	267814	129653	43	1.00
MIBI	285268	140245	43	
DTPA	216813	85616	43	**0.029**
MIBI	285268	140245	43	

ANOVA was used for analysis and Bonferroni was used for correction between each group. c-counts

Table 3.4 Alveolar clearance of the three radioaerosols

TRACER	MEAN	SD	FREQUENCY	P-VALUE
DTPA	55	8	43	
MDP	52	8	43	
MIBI	45	7	43	**<0.0001**
TOTAL	**51**	**9**	**129**	
DTPA	55	8	43	0.125
MDP	52	8	43	
MDP	52	8	43	**0.001**
MIBI	45	7	43	
DTPA	55	8	43	**<0.0001**
MIBI	45	7	43	

ANOVA was used for analysis and Bonferroni was used for correction between each group

Table 3.5 Image quality of the three radioaerosols

IMAGE QUALITY	ODDS RATIO	CI	P-VALUE
DTPA	1 (ref)		
MDP	0.42	0.17-1.01	0.052
MIBI	0.17	0.062-0.46	**0.001**
MIBI	1 (ref)		
DTPA	5.91	2.16-16.19	**0.001**
MDP	2.48	0.89-6.96	0.084

Logistic regression was used for analysis and comparison between the three groups. ref – reference, CI – confidence interval

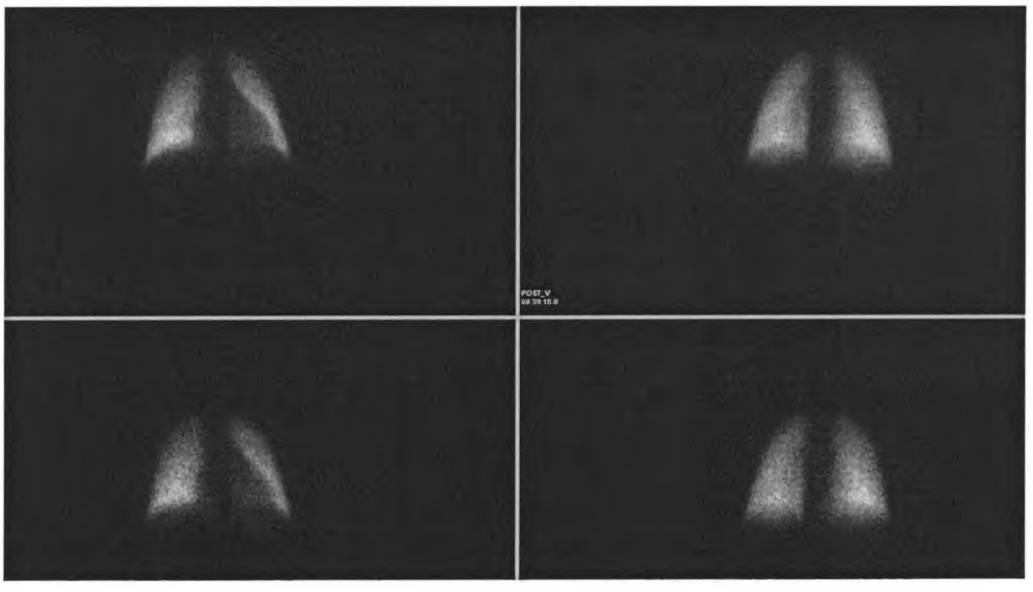

Figure 3.1 Early and late anterior and posterior ventilation images of ^{99m}Tc MIBI showing uniform and peripheral distribution of tracer with no central or stomach deposition

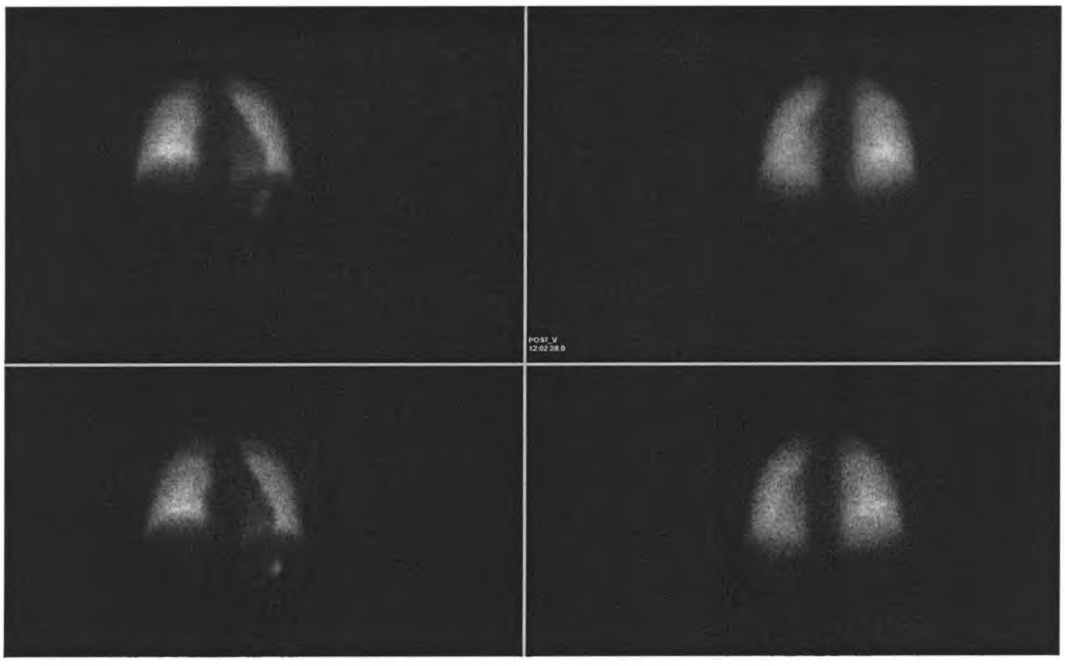

Figure 3.2 Early and late anterior and posterior ventilation images of ^{99m}Tc MIBI showing uniform and peripheral distribution of tracer with mild stomach deposition, likely due to swallowed activity

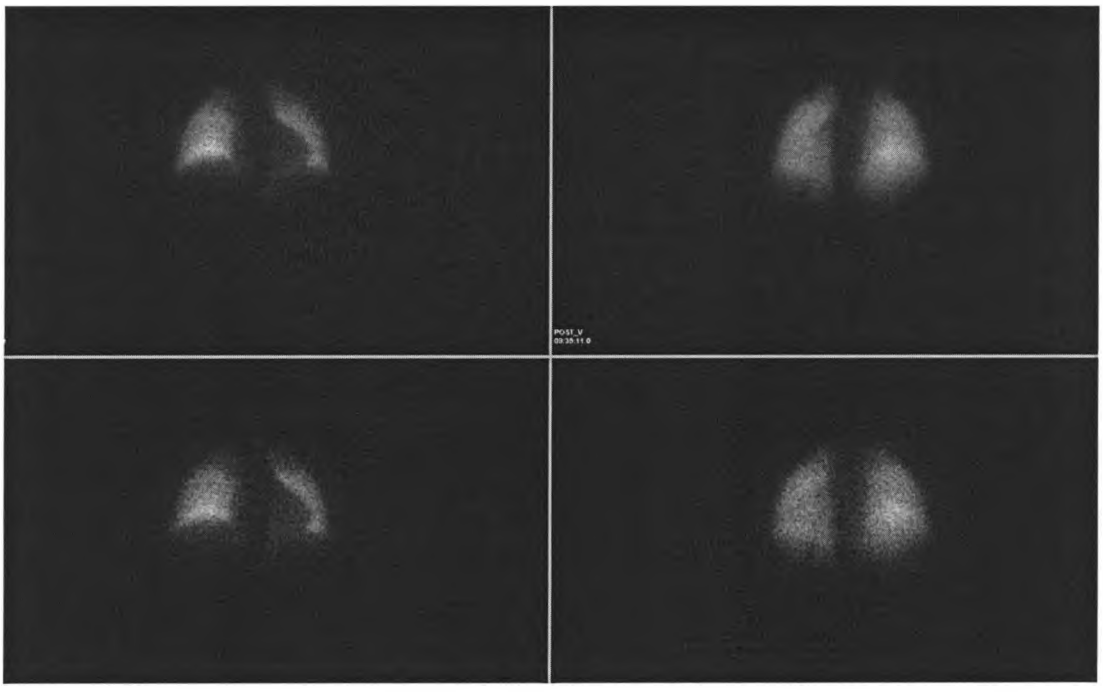

Figure 3.3 Early and late anterior and posterior ventilation images of ^{99m}Tc MDP showing uniform and peripheral distribution of tracer with no central or stomach deposition

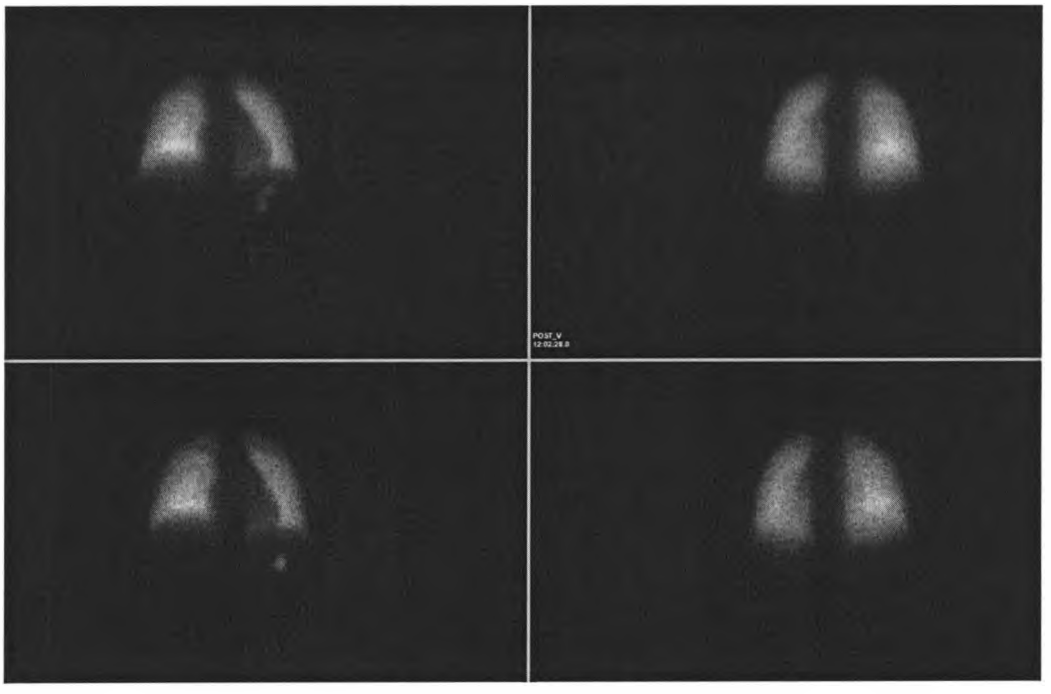

Figure 3.4 Early and late anterior and posterior ventilation images of ^{99m}Tc MDP showing uniform and peripheral distribution of tracer with stomach deposition

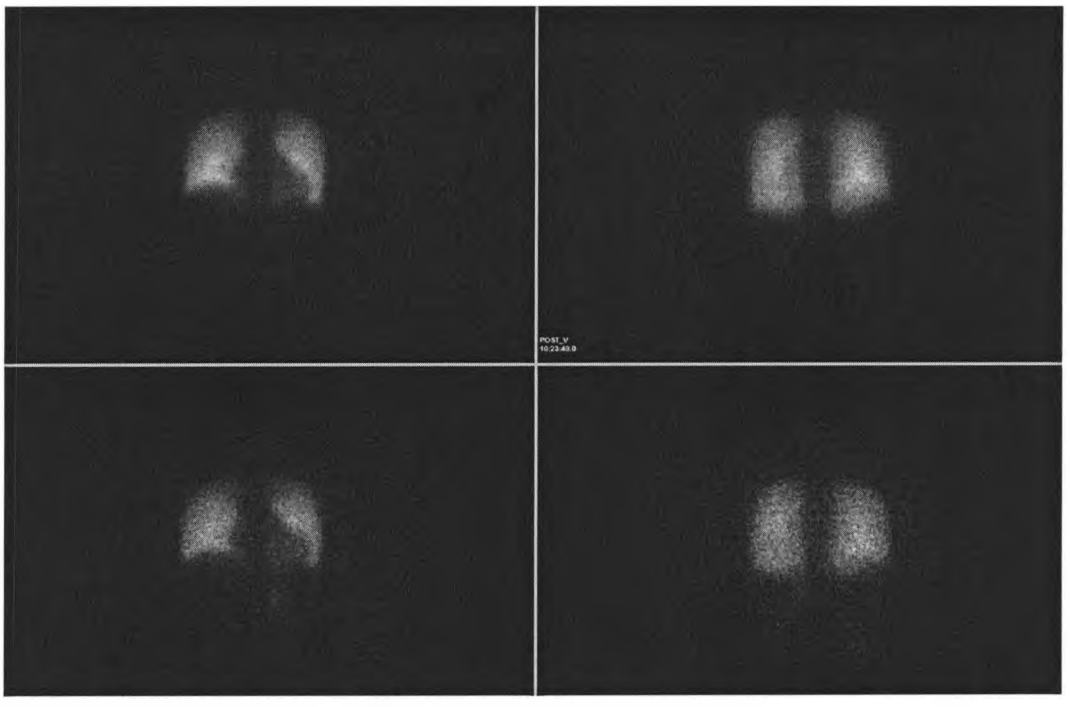

Figure 3.5 Early and late anterior and posterior ventilation images of ^{99m}Tc DTPA showing uniform and peripheral distribution of tracer.

CHAPTER 4 - DISCUSSION

A wide range of radioaerosols have been used and/or tested for lung ventilation scintigraphy. The commonest to date remains ^{99m}Tc DTPA. This study compared ^{99m}Tc MDP and ^{99m}Tc MIBI with ^{99m}Tc DTPA as lung ventilation agents to determine if they are effective tracers in lung ventilation scintigraphy, with a focus on image quality and alveolar retention of each of these radioaerosols.

None of the study participants had any adverse reactions to the radioaerosols used, for at least two hours after ventilation. Even if it is believed that most radiotracers can be aerosolized and inhaled(3), some are not without side effects. An example is ^{111}In-Cl_3 which has been shown to cause respiratory irritation leading to prolong periods of coughing.(20) This tracer however is now obsolete as a lung ventilation agent.

Our results show that ^{99m}Tc MIBI as a radioaerosol had an overall better performance than ^{99m}Tc DTPA and ^{99m}Tc MDP, with a statistically significant difference compared to the DTPA group. This observation is not different from the few studies that have compared these groups of radioaerosols.(3) MDP had better performances when compared to DTPA in a small group of patients, thus the results were not statistically significant in our study.

In this study, we showed that ^{99m}Tc MIBI had the highest mean count rates and count density amongst the three radioaerosols being investigated, with a statistically significant difference when compared to ^{99m}Tc DTPA. These results confirm findings of a smaller study by A Bhatnagara et al,(3) where they discovered that lipophilic cations like MIBI had higher nebulization rates when compared to DTPA, and this translated to significantly higher deposited radioactivity in the lungs. Although in their study only 7 participants were investigated, all of them had both MIBI and DTPA within an interval of 24 hours, with MIBI showing better count density. They explained that this higher nebulization rate and tracer deposition in the lungs when

compared to DTPA aerosol is because lipophilic cations like MIBI, when used as radioaerosols have smaller particle sizes. Due to this smaller particle size, the modern-day small sized aerosol generators will entrap less fraction of MIBI aerosols but more fractions of DTPA aerosols due to the larger particle sizes of DTPA aerosols. Isitman et al., (20) also mentioned that particle size is considered as the principal factor affecting the distribution, retention and clearance of inhaled radiotracers.

Our results also showed that the MIBI group had the slowest alveolar clearance, with a very significant statistical difference when compared to the DTPA group. This finding supports the hypothesis that ^{99m}Tc MIBI displays a slower elimination rate from the lungs following inhalation as an aerosol when compared to DTPA.(18, 22, 23) The results from Bhatnagara et al. (3), in their study suggested that lipophilic cations are trapped in the respiratory tract 3.7 times more than DTPA aerosols. However, it is expected that due to its greater lipophilicity, MIBI should have a faster clearance rate, but Rupareliaa et al. (18, 23) in two studies attributed the slow clearance of MIBI from the lungs to the presence of p glycoprotein in the lungs, which pumps the aerosol back towards the airway.

We observed that 5 participants had extremely slow alveolar clearance (mean clearance of 18% as compared to the overall mean of 51%). This was not related to a specific tracer or the smoking status of the participants. Studies have shown significantly delayed clearance of MIBI from the lungs in healthy smokers, and they attribute this to the possible upregulation of p glycoprotein in smokers due to the numerous xenobiotics in cigarette smoke.(18, 23, 24) We did not find this trend in our study as there was no statistically significant difference in alveolar clearance between smokers and non-smokers in the MIBI group. This might be due to the very few numbers of study participants in this category and it must be noted that the primary objectives of this study were not to compare smokers to non-smokers or to study lung clearance in either of the smokers or non-smokers group.

Finally, we were also able to show that the MIBI group had the best image quality with less stomach and central deposition in the airways. There was a statistically significant difference between the MIBI group and the DTPA group in this regard. This finding was also similar to the findings in the study conducted by Bhatnagara et al. (3). The improved count density and lack of deposition in the stomach and central airways with lipophilic cations lead to better lung images visually. In their study, it was assumed that unlike DTPA aerosols, MIBI aerosols do not seem to cross the alveolar epithelium – endothelium barrier and gastrointestinal mucosa, at least a few hours after inhalation. The aerosols from DTPA cross these membranes easily, leading to stomach and central airway deposition. Stomach activity seen with MIBI aerosols are usually due to secondary stomach deposition from swallowed activity.(3)

It is also worth mentioning, although not statistically significant, that MDP also performed better than DTPA, hence it passes as a good substitute for DTPA. Our findings agree with that in the literature, which claims that ^{99m}Tc phosphate compounds have high alveolar deposition and slow clearance, thus providing suitable aerosols for lung ventilation scintigraphy.(11) Isitman et al. (11) in their study compared ^{99m}Tc PYP to ^{99m}Tc DTPA and found out that PYP had slower alveolar clearance, making it an ideal agent for SPECT lung ventilation imaging. Our findings with MDP in this regard was not statistically significant. We must be aware that even if both are phosphate compounds, pyrophosphates have certain characteristics which are different from diphosphonates.

Colin and Kalpna (19) in their recent case report concluded that HDP, another diphosphonate that is very similar to MDP, enabled adequate ventilation imaging in two patients. They recommended larger studies be carried out before this agent can be officially used as a standard alternative agent to DTPA. We believe our findings in this study are sufficiently robust and enough to make these agents standard alternatives to DTPA.

It is important to know that our study was conducted using two different gamma cameras. Even though they both had the same processing software, there is no guarantee that their detectors have the same efficiency, and this could affect the precision of the study. A more accurate study would have been to use the same gamma camera for all the participants.

The dose range of radioaerosols for each subject was 20-26mCi and the time interval between the two anterior/posterior acquisition was 20-25 minutes. Although the mean dose and time interval of acquisition for the three groups was very close to the overall mean, a more effective experiment, perhaps, would have been to perform this study with narrower ranges. The most accurate results would also have been obtained if each radioaerosol was used on the same study participant, although getting ethical approval for testing each of the three radioaerosols on the same participant would have been very difficult.

However, our study has the largest number of participants, when compared to the few that are in the literature. It is also the first randomized prospective study in this regard thus being a level Ib study.(16) With our findings, using MIBI and MDP as tracers for ventilation scintigraphy in patients with suspected PTE will prove to be cost effective, as there would be no need to open a vial of DTPA for just one patient, whenever spare doses of MIBI and MDP are available.

SPECT lung ventilation imaging is becoming a common practice in most nuclear medicine facilities. It would be interesting to see if ^{99m}Tc MIBI will produce good quality images for SPECT ventilation scintigraphy. An ideal aerosol for SPECT ventilation lung imaging should have minimal central airway deposition, high alveolar deposition and slow clearance from the lungs.(11) Therefore, with the disadvantages of DTPA as an aerosol, most centers rely on the more expensive Technegas for SPECT lung ventilation imaging. Not every center has Technegas for this procedure, as it is expensive and is technically more demanding. Since our study has shown that MIBI has better alveolar retention and image quality when compared to DTPA, this tracer might be optimal for SPECT imaging. Studies can be carried out to see if this agent can be used for SPECT lung ventilation imaging, with satisfactory or excellent image quality.

CHAPTER 5 - CONCLUSION

The aim of our study was to compare three radiopharmaceuticals, which include ^{99m}Tc DTPA, ^{99m}Tc MIBI and ^{99m}Tc MDP as radioaerosols for lung ventilation scintigraphy in patients being assessed for PTE. From our study, we have shown that ^{99m}Tc MIBI and ^{99m}Tc MDP are very good substitutes for ^{99m}Tc DTPA. Of the three radioaerosols, ^{99m}Tc MIBI demonstrated the best image quality and slowest alveolar clearance. ^{99m}Tc MDP was also shown to be equally as good as ^{99m}Tc DTPA if not better, in terms of image quality and alveolar clearance. We can therefore confidently conclude that MIBI and MDP may replace DTPA as tracers for ventilation scintigraphy in patients with suspected PTE. In centers that have spare doses of these tracers readily available, their use in this regard will prove to be cost effective in the long-term. We therefore recommend with confidence that these agents should become standard alternatives to DTPA for lung ventilation imaging in patients being investigated for suspected PTE. We know that MIBI and MDP due to their slower alveolar clearance will have more radiation absorbed dose to the lungs as compared to DTPA. However, previous studies using these agents have documented that the radiation absorbed dose to the lungs is clinically acceptable and relatively safe, since approximately only 1 mCi of these agents are deposited in the lungs.(11, 18, 20)

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7. APPENDIX

7.1 Protocol for ventilation

VENTILATION PROTOCOL

- Load the generator chamber with 25mCi of radiotracer (Tc-99m DTPA, MIBI OR MDP) in 1 ml per patient.
- Patient should be positioned in the erect position (sitting) with a nose clip.
- With the tubing erect, patient should suck and blow on the mouth piece like a straw for a few seconds before pressing the start button.
- Each patient should ventilate for about 90 seconds, to get a flow rate of about 0.6 mls/min.
- After completing the procedure, patient should continue to breathe for about 20seconds before taking off the nose clip.
- Scan immediately (within at least 5 mins of completing the ventilation).

7.2 Protocol for image acquisition

VENTILATION ACQUISITION PROTOCOL

- Acquisition should start within 3 minutes of completing radio aerosol ventilation.

- Each patient should be started with, anterior/posterior acquisition, scanning for 5 minutes (300 seconds).

- Each other view will be done under 3 minutes (180 seconds) each.

- At the end of the last view, patient should remain supine for 10 minutes, and then a repeat anterior/posterior view is acquired for 3 minutes (180 seconds).

7.3 Participant information sheet and consent form

INFORMATION DOCUMENT

Study title: Comparison of three Radiopharmaceuticals for Lung Ventilation Imaging

Good Day,

Introduction:

We are doing a research on lung ventilation using three different radio tracers. Research is just the process or a way of learning the answer to a question. In this study we want to learn which radio tracer is best for ventilation imaging.

Invitation to participate:

Dr O Evbuomwan, a registrar in the Nuclear Medicine department at the CM Johannesburg hospital would like to invite you to join this study. Before you agree to take part in this study you should fully understand what is involved. If you have any questions, which are not fully explained in this information sheet, do not hesitate to ask the investigator. You should not agree to take part unless you are completely happy about the procedure involved

What is involved in this study?

This is a prospective study, and the purpose of this study is to assess three different agents used in lung ventilation imaging. Two of these agents are not routinely used, but previous studies have shown them to have advantages over the commonly used agents. These two agents are cheaper and/or more cost effective to the hospital. Only one of the three agents would be administered to you, so there is no need to be worried about extra radiation dose. The choice of the agent to be used has been based on random selection. The usual imaging time would be increased by about 10 minutes, so the imaging time will take about 30 minutes as against 20 minutes. This research will not affect your management in any way. You do not need to fill a questionnaire for this study.

There will be no cost to you by accepting to participate in this study. Should you decline your consent, your treatment will not be affected and your decision will not influence your future care and continued treatment within this hospital.

There will be a total of 120-135 patients in this study, and all patients will be from South Africa. The study does not involve another population group from other countries.

Side effects using other agents have been documented, but no risk whatsoever has been documented using any of these agents, as previous studies have shown that these agents are safe.

By being in this study, we would be able to tell which agent is best for ventilation imaging.

Efforts will be made to keep personal information confidential. Absolute confidentiality cannot be guaranteed. Personal information may be disclosed if required by law.
Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the Research Ethics Committee and the Medicines Control Council (where appropriate).
If results are published, may lead to individual / cohort identification.

Contact details of REC administrator and chair – For reporting of complaints / problems contact
Mr Langutani Masingi, Administrative Officer: Human Research Ethics Committee (Medical)
Tel: 011 717-1234/2656
E-mail: langutani.masingi@wits.ac.za

For further information please contact Dr Evbuomwan on 0742869731

Thank you for your time.

Written Consent Form

STUDY TITLE: Comparison of three Radiopharmaceuticals for Lung Ventilation Imaging

Name of Patient.....

Patient Number.....

The aims and procedures of this study have been explained to me by the doctor. I have read and understood the subject information sheet provided.

I have had the opportunity to ask questions and to consider the answers given to me.

I understand that participation in this study is voluntary, that I may decline my consent and if I choose not to participate my decision will not affect my care and future visits at the hospital.

I hereby freely give my informed consent to taking part in this study.

NAME: .....

DATE: .....

SIGNATURE: .....

I confirm that I have fully explained the nature of the study and the procedure to be performed to the above-named patient.

NAME: .....

DATE: .....

SIGNATURE: .....

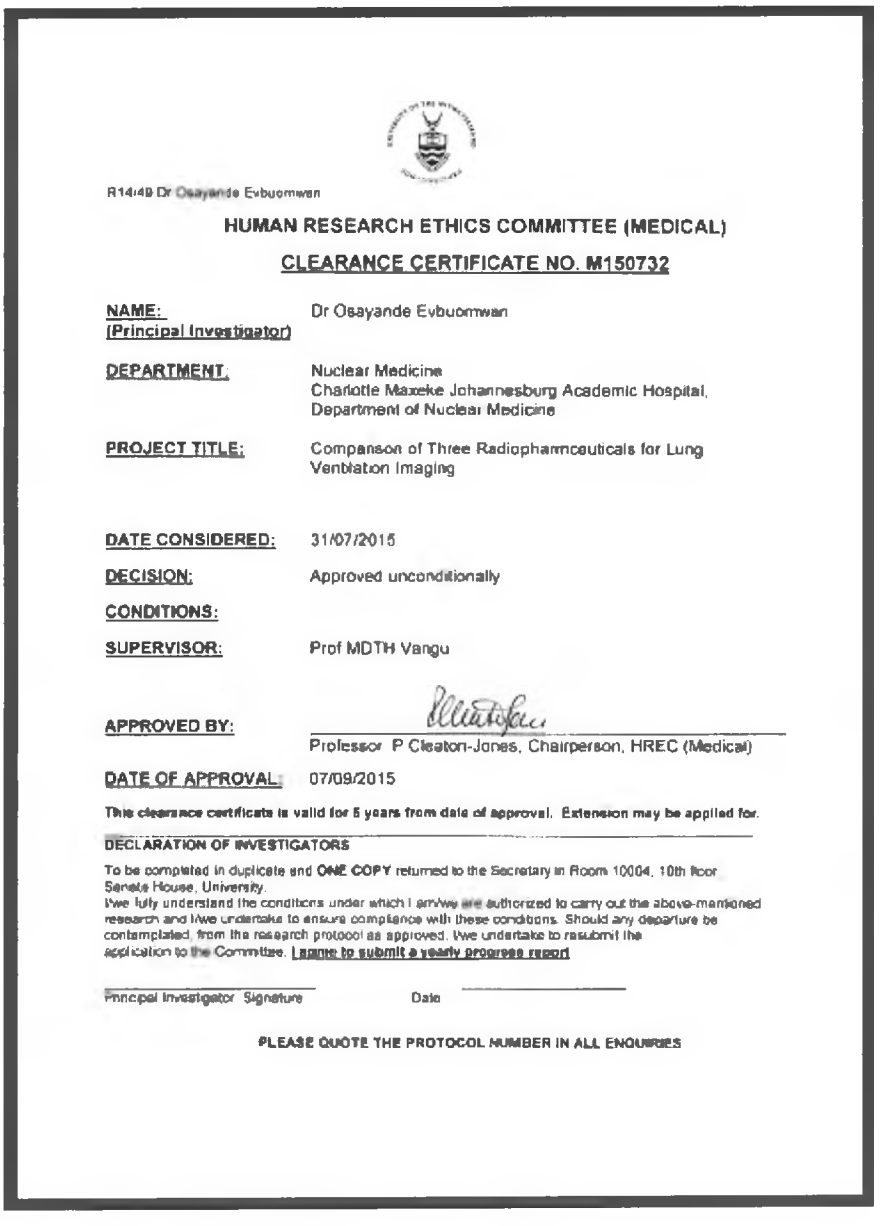
COPD –

CURRENT SMOKER –

FORMER SMOKER –

NON-SMOKER -

7.4 Ethics clearance certificate



R14/49 Dr Osayande Evbuomwan

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M150732

NAME: (Principal Investigator)	Dr Osayande Evbuomwan
DEPARTMENT:	Nuclear Medicine Charlotte Maxeke Johannesburg Academic Hospital, Department of Nuclear Medicine
PROJECT TITLE:	Comparison of Three Radiopharmceuticals for Lung Ventilation Imaging
DATE CONSIDERED:	31/07/2015
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof MDTH Vangu

APPROVED BY: _____

Professor P Cleaton-Jones, Chairperson, HREC (Medical)

DATE OF APPROVAL: 07/09/2015

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report.**

Principal Investigator Signature _____ Date _____

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES