Lung Ventilation Studies with Technetium-99m Pseudogas

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Technetium-99m Pseudogas is an ultrafine near monodisperse aerosol of 0.12-μm diam particle size. This report describes initial clinical experiences with 27 patients referred for investigation of suspected pulmonary embolism, and in whom Pseudogas ventilation images were compared with a high quality commercial aerosol. An additional group of ten patients with severe COPD was examined in a comparative trial of Pseudogas with ^{81m}Kr. Pseudogas was better than a conventional aerosol in reaching a diagnosis of pulmonary embolism using a simple blinded comparison with coded images. In addition, bronchial deposition was minimal unless COPD was severe. Moderately well patients had no difficulty inhaling the necessary activity in one or two breaths, and even severely ill and frail aged persons could accomplish the passive breathing maneuver in less than a minute. Clearance of Pseudogas was directly to the systemic circulation with a half-time of 10 min in normal subjects extending up to 100 min in patients with airways disease.

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Since Taplin and colleagues (*1*) first demonstrated the effectiveness of an aqueous aerosol labeled with technetium-99m (^{99m}Tc) as a suitable agent for lung ventilation studies, there have been many reports in the literature demonstrating both the efficacy (*2,3*) and the limitations (*4–6*) of this technique. Refinements have also appeared regularly in the literature (*7, 8*).

Radioactive gases are in widespread clinical use but there are practical problems, particularly availability of krypton-81m (^{81m}Kr), cost, contamination, radiation dose and image quality (*9,10*).

Much of the criticism of aerosol systems, particularly simple nebulizers based on the Bernoulli-effect, has been the result of the wide and skew distribution of particle sizes. The advantages of a relatively simple ^{99m}Tc-based ventilation agent has prompted recent commercial production of nebulizers with heavy filtration of the output mist to select only the smallest droplets (1–2 μm) for inhalation. However, only a small fraction (typically 5%) of the radioactive reservoir solution is inhaled and ventilation is prolonged (*11*).

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We have developed an ultrafine, near-monodispersed aerosol, (0.12 μm diam; 1.25 geometric s.d.) which has been named "Pseudogas." An initial report on the methods of production and physical properties has been published (*12*). In this paper we examine preliminary clinical data from a patient trial of Pseudogas, comparing it with a commercial [^{99m}Tc] aerosol* and ^{81m}Kr.

MATERIALS AND METHODS

Pseudogas is generated when a flammable spray of ^{99m}Tc in solution is burned. It is effectively the labeled exhaust products of this combustion. In the prototype apparatus used for these clinical studies, ~ 1 ml of ethanol containing ~ 5 mCi ^{99m}Tc was nebulized in a simple carburator system and the mist ignited by a high frequency electric arc. The air mixture was adjusted to reduce carbon monoxide levels to 50 ppm. The whole system was driven from a small domestic air compressor and produced a steady clean flame ~ 10 cm long. No oxides of nitrogen were detected in the combustion products, which filled a standard anesthetic rebreathing bag. Much of this volume consisted of air needed to nebulize the ethanol in the Bernoulli-effect process, and only 0.8 l of CO_2 was generated.

For clinical studies, the bag was uncoupled from the burner and transferred to a simple breathing circuit, consisting of a standard anesthetic mask held on by the patient over nose

and mouth. Two disposable one-way valves passively accepted Pseudogas from the bag on inhalation and directed exhaled breath to a resin wool absorbing pad. Radioactivity was trapped totally within a 60 cm^3 wad of this material.

The gas/air Pseudogas mixture was allowed to cool for about 3 min, from 45°C following the burn to 25°C, before inhalation. This temperature gradient between the Pseudogas and the bronchial walls (37°C) inhibits its diffusion and adhesion to the walls until it has equilibrated with body temperature in the lung periphery. There is a complex interaction between diffusion processes in particles having orders of magnitude more mass than the energetic air molecules near the walls of conducting airways, and net flow of aerosol through the airways. But as long as the initial temperature difference is present, little or no central deposition will be seen in patients with poor inspiratory flow rates.

All patients were studied first by Pseudogas inhalation, and imaging, with a standard four view sequence. After an interval sufficient for the tracer to clear from the lungs (typically 30 min), the procedure was repeated using the commercial [^{99m}Tc]diethylenetriaminepentaacetic acid (DTPA) aerosol. Inhalation was performed, as for Pseudogas, with the patient seated in front of the gamma camera and continued until an adequate count-rate (1.5 kc/s) was observed (2–3 min). This signal corresponded to about 0.5 mCi in the lung. Perfusion lung scans then followed injection of 5 mCi [^{99m}Tc]macroaggregated albumen (MAA).

Twenty-seven patients referred with suspected pulmonary embolism were included. There were 19 females and eight males ranging in age from 17 to 92 yr. Nine patients were known to have concurrent chronic obstructive pulmonary disease (COPD) either on clinical assessment, x-ray abnormalities, or respiratory function testing. The remaining 18 consisted of either postoperative patients or those presenting with pleuritic chest pain.

Thyroid uptake and mucosal secretions of ^{99m}Tc were inhibited by administering 600 mg potassium perchlorate before Pseudogas inhalation. Ventilation and imaging maneuvers were done in the sitting position except where incapacity precluded it (three cases). All images were recorded on film for interpretation. Pseudogas images and the posterior aerosol view were also acquired as static frames on computer (DEC PDP 11/34, "Gamma-11") for calculation of clearance rates in ten patients. All ventilation views were acquired for 300 counts per cm^2, and perfusion views 1k count per cm^2, measured where activity was perceived to be a maximum.

An additional group of 11 patients and four normal subjects was studied at our institution where ^{81m}Kr gas was used for comparison. In this selected group of inpatients whose ages ranged from 61–79 yr there were eight males and two females. Five males had chronic airflow obstruction, two had emphysema, one had bronchiectasis, and one, asthma. Both females had chronic asthma. Posterior gamma camera images of the lungs were obtained using both ^{81m}Kr and Pseudogas.

RESULTS

Pulmonary embolism was diagnosed in nine patients as shown by the criterion of at least one mismatched perfusion/ventilation defect of segmental size. Two experienced nuclear medicine physicians found, on the basis of image comparison alone, (when presented with coded sets of ventilation/perfusion studies), that Pseudogas was better than conventional aerosols in reaching a diagnosis of pulmonary embolism.

This observation was confirmed by a quantitative measure of the ventilation images (Fig. 1). A vertical slice profile five cells wide was taken through the apex of the right lung on the anterior or posterior image in the ten patients for which computer data were available. Thresholds were set at 20 and 50% of the maximum (five cell wide) pixel activity. The distance between corresponding threshold intercepts on the profile was measured for both Pseudogas and aerosol and expressed as a ratio for each patient to give a representation of image size. These ratios ranged from 1 for clinically normal images to 1.7 for grossly abnormal images, at the 20% point. The 50% point analysis showed closer correlation between the two agents. Thus, Pseudogas gave better visualization of the lung periphery with evidence of reduced central airway trapping.

Bronchial deposition of aerosol presented more interpretive problems than with Pseudogas (Fig. 2). Bronchial deposition of Pseudogas was minimal, unless COPD was severe. A small amount of blood background activity appeared in the later

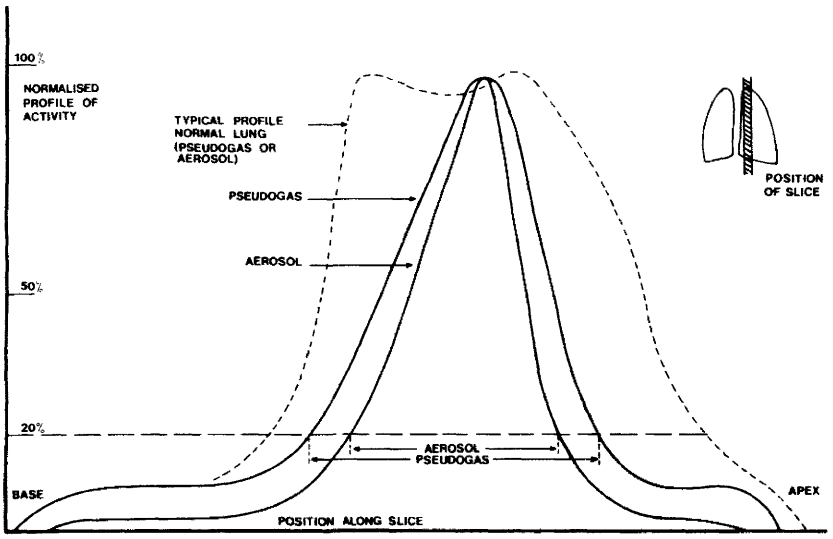

FIGURE 1
Normalized vertical slice profile through right lung of patient with severe parenchymal lung disease. Slice from representative normal lung is added for reference

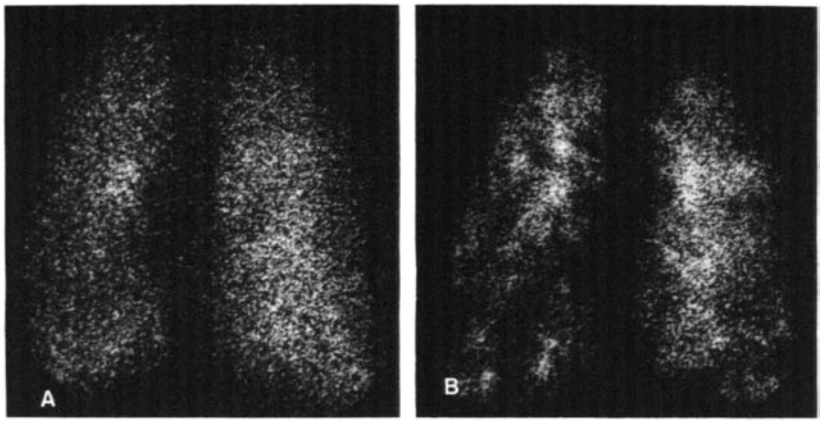

FIGURE 2
Posterior views from 45-yr-old female with severe COPD and secondary polycythemia. A: Pseudogas ventilation. B: DTPA aerosol ventilation

Pseudogas images as the tracer was cleared from the lungs, but this did not interfere with image interpretation (Fig. 3). Quantitative data analysis showed that Pseudogas moved directly from the lungs (presumably through the alveolar-capillary membrane) into the systemic circulation with a clearance half-time of 10 min (8.6–11 min) in six normal subjects. In patients with airways disease, half time clearance was increased—in one asthmatic to 100 min. The clearance rate was nonuniform in these patients and correlated with the severity of the disease (Fig. 4).

Detailed results of the ^{81m}Kr comparison study will be presented elsewhere. The distributions of ^{99m}Tc in the four normal subjects were similar to those of ^{81m}Kr, but there was a higher concentration in the caudal regions relative to the cranial regions than there was in the ^{81m}Kr images (Fig. 5). The Pseudogas image of every patient (all of whom had very severe COPD) contained regions of high count density that did not appear in the ^{81m}Kr image and are due to bronchial deposition.

These regions, which varied in number and size among the 11 patients, distorted the images of the lung fields (Fig. 6), although quantitative analysis showed the overall distribution of radioactivity to be otherwise similar.

DISCUSSION

Clearly, the major advantage of Pseudogas as a ventilation agent is that particle size is an order of magnitude smaller

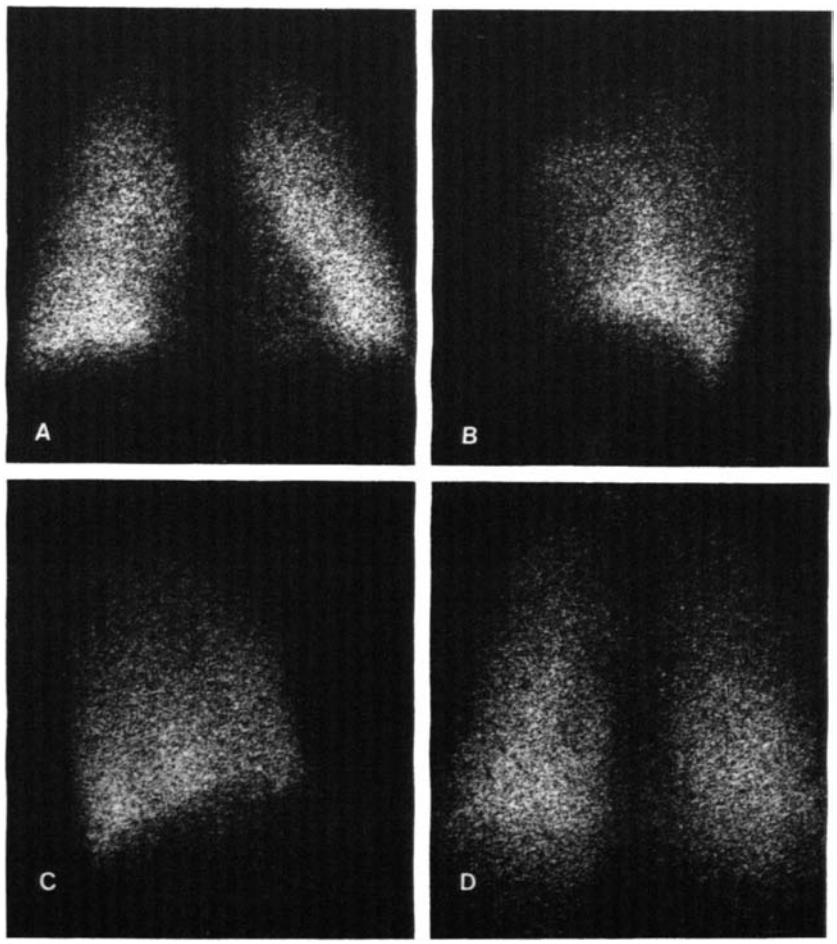

FIGURE 3
Four standard views following single-breath pseudogas inhalation in 22-yr-old male with unexplained dyspnoea. Images A–D were acquired sequentially following inhalation over total time period of 6 min

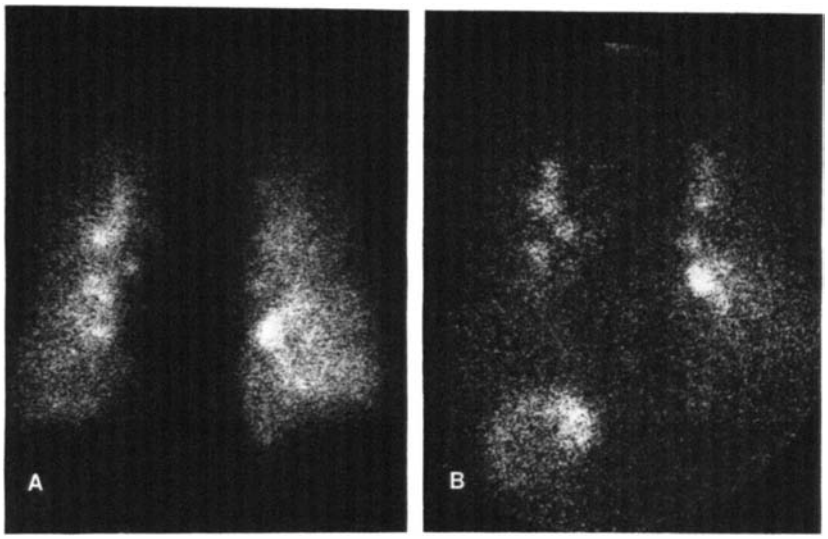

FIGURE 4
Initial and delayed (22 min) images from 51-yr-old male heavy smoker with history of recent left basal pneumonia, hemoptysis, pleural rub, and CXR evidence of atelectasis. Note: Gastric mucosal secretion and thyroid uptake are strongly evident in this patient because pretest perchlorate administration was accidently omitted

than conventional aerosols, coupled with greatly increased number of labeled particles per unit volume of carrier gas. Pseudogas behavior is dominated by diffusion kinetics with only minimal deposition by sedimentation and impaction. Significant deposition in conducting airways was only seen in severe COPD.

Regions of high count density in the images of [^{99m}Tc] Pseudogas masked an overall similarity of its distributions to ^{81m}Kr. Some investigation may be worthwhile into the clinical significance of and varying clearance rates from such regions of high density deposition of [^{99m}Tc] aerosols in abnormal lungs.

The net efficiency of the present prototype unit as a ratio of activity delivered to the lungs from the activity originally "burned" is 30%. Further refinement of burner design—in particular, a better controlled initial aerosol ignition system that prevents any unburned mist escaping to deposit on the burner walls—will easily raise this figure above 50%. By comparison, heavily filtered Bernoulli-effect nebulizers return an equivalent efficiency ~5%.

Detailed analysis of the chemical nature of the Pseudogas particles has not been done, but it is thought to be technetium heptoxide with two hydration shells surrounding each molecule. This is supported by the observation that if Pseudogas is kept at 40°C for 30 min and a particle size analysis performed, a second species of particles having a mean diameter of 0.02 μm is created—consistent with the shedding of one hydration shell (*13*). Conversely, it should be a simple matter to use Pseudogas as nuclei for a La Mer generator (*14*) and "grow" ^{99m}Tc-labeled water vapor to any convenient, controllable size. This will produce an agent for functional imaging procedures of the upper airways and sinuses.

Because Pseudogas is cleared across the alveolar-capillary membrane, its clearance rate is dependent on pulmonary blood flow and the physiology of membrane transport. Complex mechanisms are involved, but it should be possible to extract valuable clinical data from differences in whole lung and regional clearance rates.

FOOTNOTE

* Nuclear Accessories Pty. Ltd.

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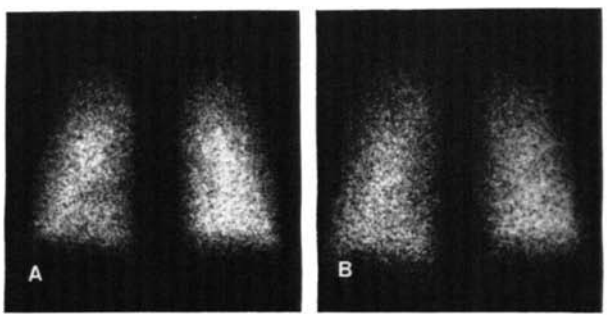

FIGURE 5
Posterior images from normal volunteer. A: ^{81m}Kr, B: [^{99m}Tc]Pseudogas

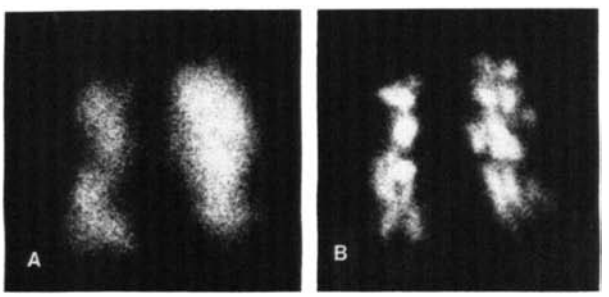

FIGURE 6
Patient with severe chronic COPD. A: ^{81m}Kr, B: [^{99m}Tc]Pseudogas

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