Physical Properties and Use of Pertechnegas as a Ventilation Agent

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Pertechnegas, a variant of technegas, produces similar ventilation images with a much increased clearance rate. This work aims to determine the properties of pertechnegas and its use as a ventilatory agent. Methods: Fourteen men and 11 women were scanned for PE after pertechnegas ventilation. Six were reimaged with technegas within 1 wk. Studies were reported according to PIOPED criteria. Pertechnegas samples were analyzed by transmission electron microscopy (TEM), cascade impaction (CI), aerosol mobility analysis (AMA), Fourier transform mass spectrometry (FTMS), x-ray photoelectron spectroscopy (XPS), paper strip (PC) and gas chromatography (GC). Results: Post-test probabilities were normal in 5, low in 8, high in 3 and indeterminate in 7. There were 15 Grade 1, 6 Grade 2 and 4 Grade 3 studies. All Grade 3 patients had FEV<sub>1</sub> < 1.5 liters, 3 with rates < 1.0 liter. Patients with high probability had proven deep venous thrombosis in three by venography and in one by doppler. TEM identified 0.3 μm salt particles. CI demonstrated a 7-min time to half clearance from the chamber for particles in the < 0.1 μm range. AMA indicated salt particles were < 0.032 μm when salt was excluded. Pertechnegas behaves in PC as pertechnetate. GC demonstrated CO levels below 516 ppm. CO<sub>2</sub> concentrations were 0.146 ± 0.0009%. FTMS found molecular pertechnetate species including <sup>99m</sup>TcO<sub>3</sub>(OH)<sup>+</sup>, <sup>99m</sup>TcO<sub>2</sub>(OH)<sup>2</sup> and Na<sup>99m</sup>TcO<sub>4</sub>(OH)<sub>2</sub>. XPS confirmed that these Tc species exist in oxidation state +7. Conclusion: Comparison with technegas images in the follow-up group proved equivalent in the first five views, but indistinct lung boundaries and a high background activity characterized the final anterior images. The active component of pertechnegas is molecular pertechnetate.

Key Words: pertechnegas; lung ventilation; x-ray photoelectron spectroscopy

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Pertechnegas is a serendipitous agent discovered as a variant in the production of technegas. The addition of 2%-3% oxygen to the argon atmosphere in which the carbon crucible containing Na<sup>99m</sup>TcO<sub>4</sub> is heated, results in the production of an agent with the same ventilatory properties as technegas, but one crucial difference. It clears from the lungs with a half-life of approximately 7-10 min (1). In contrast, technegas clears with the physical half-life of <sup>99m</sup>Tc. This group has reported its use in the early detection of interstitial lung disease, and explored its similar physico-chemical behavior to vaporized Na<sup>99m</sup>TcO<sub>4</sub>

Earlier work with pertechnegas demonstrated similar properties to technegas with respect to ease of ventilation and the production of images with good peripheral penetration, little central airways deposition and high count densities. This observation was intriguing, given the fundamental physiologiccal difference between the rates at which the agents cleared from the lungs.

We undertook further evaluation of pertechnegas's physical and chemical characteristics and its utility as a ventilatory agent. Comparison with technegas ventilatory imaging was made in a small series of patients. Chemical analysis included cascade impaction (CI), aerosol mobility analysis (AMA), transmission electron microscopy (TEM), Fourier transform ion cyclotron resonance mass spectrometry (FTMS), x-ray photoelectron spectroscopy (XPS), paper strip (PC) and gas chromatography (GC).

MATERIALS AND METHODS

Subjects

Twenty-five patients (14 men, 11 women) were prospectively studied. The average age of the patients was 62.3 yr, with a range of 22-81 yr. All patients were scanned for suspected pulmonary embolism. Chest radiography, arterial blood gases and d-dimer levels were obtained for all patients. If clinically indicated, lung function studies and venography and/or duplex doppler studies of the lower limbs were also undertaken. Repeat imaging with technegas was performed in six patients within 1 wk of the initial study.

Patient Studies

All patients were initially ventilated with pertechnegas, prepared as has been described elsewhere (1). Briefly, 650-900 M bq Na<sup>99m</sup>TcO<sub>4</sub> were heated to 2500°C in a graphite crucible under an atmosphere of 3% O<sub>2</sub> and 97% Ar. Technegas was similarly manufactured by heating the crucible and tracer in a 100% argon atmosphere. Patients were ventilated in the supine position with a large field of view gamma camera placed beneath the posterior lung fields. In general, 2-5 breaths were required to attain a counting rate of 2000-3000 per second. Each ventilation image was acquired for 30 sec with total counts ranging from approximately 100K to 30K, depending on the ease of delivery and specific activity of the agent. After collection of the six ventilation images (L Lat, LPO, R Lat, RPO, Ant and Post), the patient was injected with 190-220 MBq <sup>99m</sup>Tc-macroaggregated albumin (MAA). Images were then acquired for a preset time of 30 sec per projection.

Reporting Criteria

All clinical studies were reported by two experienced physicians who were blinded. The PIOPED criteria were used for reporting the post-test probabilities of embolic disease. Ventilatory images were qualitatively classified on a scale of 3. Grade 3 was associated with significant central airway deposition and disruption of peripheral activity with loss of definition in the lung. Grade 2 was significant central airways deposition with good peripheral distribution. Grade 1 was a normal study.
Sample Preparation for Particle Sizing and Chemistry

All samples were generated in a commercial technegas generator under a 3% oxygen, 97% argon gas mixture with 0.1 ml of Na\(^{99m}\)TcO\(_4\) eluate in the crucible heated to 2,500°C at 1100 kPa. For spectrometry, concentrated Na\(^{99m}\)TcO\(_4\) eluate was used to increase the number of technetium containing species to \(10^8-10^{19}\) molecules/cm\(^3\). Where noted, NH\(_2\)TcO\(_4\) was used in order to eliminate spectral interference from Na auger electron lines.

Sample Analysis

Pertechnegas was generated and immediately drawn through a four-stage cascade impactor (CI) at 1 liter/sec. All stages and the trapping filter were counted on a gamma camera. This was repeated three times with sampling at 7, 12 and 30 min after generation.

Another pertechnegas sample was generated and immediately drawn through a Whitby Aerosol Mobility Mass Analyzer (AMA) at 1 liter/sec and the particle size distribution determined. As a control, the generator was carefully cleaned to remove salt and analysis was repeated with a fresh crucible devoid of isotope.

Pertechnegas was collected by impaction onto a carbon grid and imaged by TEM at a magnification of 30600. Particulates observed were subjected to analysis by electron energy loss spectroscopy (EELS).

The Spectrospin CMS-47X Fourier transform-mass spectrometer (FTMS) (electron impact, 70 eV) used in this work has been described elsewhere (2,3). Pertechnegas generated from concentrated Na\(^{99m}\)TcO\(_4\) was introduced into the instrument via a heated leak valve through a 1.5-m length of 6-mm diameter evacuated nylon tubing. The pressure of pertechnegas in the FTMS was approximately 2 to \(4 \times 10^{-7}\) mbar.

The x-ray photoelectron spectra (XPS) were recorded on a spectrometer using both Al K\(\alpha\) (1,487 eV) and Mg K\(\alpha\) (1,254 eV) x-ray sources. As reported in (4), a stainless steel probe or silver shim was suspended inside the generator, approximately 6 cm above the carbon crucible to collect samples of pertechnegas. XPS studies were performed with minimal delay between generation and analysis to minimize exposure to air. The O 1s (532 eV) and C 1s (284 eV) photoelectron peaks were used to calibrate the Tc-3d peaks. The difference in binding energies of the spin-orbit split peaks of 3.6 eV was used to positively identify technetium in XPS spectra. Binding energies quoted are the mean for the spin-orbit split technetium 3d values i.e., (J = 3/2 + J = 5/2)/2. Here, J represents the sum of spin and orbital angular momenta of the particular 3d electrons.

Activity from fresh pertechnegas introduced into an evacuated 500-ml glass bulb was estimated using a gamma camera. Solution of the \(^{99m}\)Tc in the bulb was subsequently attempted using distilled water (20 ml). After vigorous washing, the water was decanted and retained. The radioactivity remaining in the bulb was then estimated as before. The solution retained was then subjected to paper strip chromatography developed in acetone. Migration of the \(^{99m}\)Tc was measured in a gamma well counter.

CO\(_2\) and CO\(_2\) concentrations in fresh pertechnegas were analyzed in a gas chromatograph.

RESULTS

Patient Studies

The patient studies were classified according to post-test probability of pulmonary thromboembolic disease as normal in 5, low in 8, high in 5 and indeterminate in 7. Typical pertechnegas images are illustrated by a normal study in Figure 1, a high probability study with matched and mismatched segments in Figure 2 and an indeterminate probability study in Figure 3. Those patients with a high probability study had proven deep venous thrombosis in three by venography and in one by doppler studies. Chest films were all normal, with arterial blood gas A-a gradients being abnormally increased in two. D-dimer levels were elevated in four. In the indeterminate group, three patients had normal contrast venography and two normal doppler ultrasounds. D-dimers were elevated in three patients and six had elevated A-a gradients. Chest films were abnormal in five, with three patients displaying atelectasis, two consolidation and four evidence of hyperexpansion and parenchymal cystic changes. The normal and low probability groups had no significant changes in chest films or D-dimer levels. Two had elevated A-a gradients. Follow-up for 1 yr found recurrent embolic disease in two patients with an initial diagnosis of pulmonary emboli. One patient with an indeterminate lung study and carcinoma of the breast died of metastatic lung and brain disease.

Qualitative analysis of the ventilation studies showed 15 were Grade 1, six Grade 2 and four Grade 3. All patients with Grade 3 changes had forced expiratory flow rates (FEV\(_1\)) in the first second of less than 1.5 liters, three with rates less than 1.0 liter.

Particle Analysis

The CI results (Fig. 4) show that immediately after generation, 80% of the labeled particles are <0.1 \(\mu\)m and the remaining 20% are in the range 0.1–1.0 \(\mu\)m. At 7 min postgeneration, 30% are >0.7 \(\mu\)m with dominance of the 0.7–1.0 \(\mu\)m range at 30 min.

The distributions determined from the AMA show that immediately after generation, 98% of the particles from the control crucible were in the <0.032 \(\mu\)m range, whereas 90% of
pertechnegas particles were 0.31–0.1 μm and 9% were 0.31–0.1 μm.

Particles observed under TEM on the carbon grid ranged from 0.1–0.4 μm with the majority around 0.3 μm. These particles were unstable under the electron beam at high magnification. EELS spectra identified these as NaCl.

Figure 5 shows a typical positive-ion 70eV electron impact FT mass spectrum of pertechnegas. The spectrum indicates that the ground state 99mTc-oxide species 99mTcO2(OH)+ and 99mTcO2(OH)2+ at m/z 164 and 182 are present in very low concentrations relative to Ar+ (estimated <5 × 10^{10} molecules/cm^2 of technetium-based particles). These two ions have been observed in previous Knudsen effusion mass spectrometric experiments by Gibson (5). The small peak at m/z 205 could be assigned to Na99mTcO2(OH)+ or 99mTc(OH)2(H2O)+ by Gibson has reported observing the related K99mTcO2(OH)+ we assign this ion at m/z 205 to Na99mTcO2(OH)+.

A chemical shift of 261.8 eV was observed for the pertechnegas particulates collected on a stainless steel probe tip (Curve A, Fig. 6). This corresponds to technetium in oxidation state +7 (6) and compares well with the chemical shift of 262.5 eV observed for NH499mTcO4 on a silver shim (Curve B, Fig. 6).

Chromatography of the solution of pertechnegas in water suggested that the agent was in the form of pertechnetate or water soluble 99mTc-oxides, and behaved in paper chromatography experiments as pertechnetate. Further measurements demonstrated that over 90% of the activity had been washed from the bulb into the water.

Gas chromatography of five separate samples demonstrated that CO levels were below the determinable limit of the instrument (i.e., less than 516 ppm). Average CO2 concentrations were 0.146% ± 0.009%.

FIGURE 2. Pulmonary emboli. A 46-yr-old woman with metastatic breast carcinoma and a large malignant pleural effusion on the right side. She became acutely short of breath. Venography demonstrated extensive deep venous thrombosis. The ventilation images are shown in rows one and three. The study demonstrates an extensive matching ventilation and perfusion defect in the right lung and several segmental unmatched perfusion defects in the radiologically normal left lung.

FIGURE 3. Indeterminate study. A 74-yr-old man with chronic obstructive lung disease. He became acutely dyspneic. The study shows extensive matching nonsegmental disruption in ventilation and perfusion. Chest radiograph demonstrated extensive parenchymal disease and spirometry and blood gas analysis was also abnormal, with the pattern supporting chronic obstructive airways disease. The ventilation images are shown in rows one and three.
FIGURE 5. A positive-ion 70-eV electron impact FT mass spectrum of gas phase pertechnegas after generation from 0.1 ml of NaTcO₄ in 3% O₂-97% Ar.

FIGURE 6. Al-Kα x-ray photoelectron counts v/s binding energy (BE) in eV of (Curve A) a pertechnegas thin film deposited on stainless steel after generation from 0.1 ml of NH₄⁹TcO₄, (Curve B) a thin film of NH₄⁹⁹TcO₄ deposited on a silver shim.

DISCUSSION

The current study confirms the utility of pertechnegas as a ventilatory agent that is at least as good as technegas. Qualitative scoring of the images by the two readers gave consistent results, with 60% of images having no significant central airway or peripheral disruption and only 16% exhibiting some degree of image degradation due to these problems. The problems were encountered in patients who had FEV₁ of under 1 liter and radiological evidence of parenchymal disease. It confirms retention of the important ventilatory capabilities of technegas. In particular, the ease of ventilation with 2–4 breaths and the attainment of high counting rates with little image degradation was clearly demonstrated.

Comparison of the ventilation images with technegas in the follow-up group of patients gave equivalent images in the first five views, but indistinct lung boundaries and a high background activity in the final anterior image. This is not surprising, as the final image would have been acquired after 1.0–1.5 half clearance times of pertechnegas. The rapid clearance of pertechnegas from the lungs mandates careful attention to the order in which the study is acquired, if images of diagnostic quality are to be achieved. We routinely acquired projections with the highest information content first (i.e., the posterior oblique and lateral views). These allowed visualization of the highest number of segments (7) in the early phase of the study. The final image was invariably of the poorest quality, but in all studies this was the anterior projection, one of the least useful views in terms of the delineation of the segmental anatomy of the lungs. The illustrations clearly demonstrate that it is in this final image that the thyroid activity is maximal. Count density in the lungs is consequently lowest in this image.

The clinical observation of the good imaging qualities of pertechnegas implies that the particle sizes should be comparable with technegas. We found the median particle size to be in the 0.03–0.1 μm range, which is comparable with measurements for technegas by this group and similar to those of Lemb et al. (8) who found 97 nm using photo correlation spectroscopy. This range is lower, however, than results obtained from diffusion battery measurements by Strong and Agnew (9), who found the median diameter for technegas to be 140 nm and more recently Lloyd et al. (10) who found similar median diameters for both technegas and pertechnegas at 158 nm and 167 nm, respectively. As can be seen in Figure 4, the Cl fraction under 0.1 μm disappears rapidly from the microaerosol rendering the generator output much less useful after the 10-min cutoff point. The AMA results clearly show the size difference when salt is carefully excluded from the generator.

TEM demonstrated particles of 0.1–0.4 μm which EELS spectra identified as NaCl. This agrees with the findings of Lloyd et al. (10) and is not unexpected given that ⁹⁹mTc is eluted as Na₉⁹mTcO₄ with normal saline. Therefore, NaCl is in excess of technetium in the crucible by many orders of magnitude. Salt has a vaporization temperature of 1413°C (11) and will have been completely vaporized and condensed into the cold buffer gas long before the final crucible temperature of 2500°C. Therefore, most reported particle sizes of both technegas and pertechnegas are almost certainly due to the vaporized salt rather than the carbon or technetium. It is highly probable
that the radioactive agent is associated with the aggregates of sodium chloride, as the salt particles are of a size that allows good diffusion to the alveolar level.

Support for this hypothesis is found in the work of Friedlander (12). He observed that there is an optimal size for the transport and deposition of particulate matter in the gas exchange units of the lungs. Particles that are less than 0.2 μm avoid deposition by the mechanisms of sedimentation or impaction in the bronchial tree while particles less than 0.05 μm are increasingly governed by diffusion. As pointed out by Strong and Agnew (9), diffusion governed particles are likely to travel to a surface of the delivery tubing and deposit before reaching the patient. Friedlander demonstrated that the mean free diffusion distance for particles of less than 0.001 μm is a matter of millimetres. This is approximately the particle size of technegas when it is measured in the salt free carrier state, as reported by Burch et al. (13).

The behavior of pertechnegas at the alveolar level is profoundly different to technegas. There is no effective clearance of technegas from the lungs, other than the rate of decay of the activity of 99mTc. Pertechnegas, however, clears from the lungs with a half-life of approximately 7–10 min.

The mass spectrometry provides direct evidence that a variety of gas phase technetium oxides are present in the pertechnegas vapor. The most probable reaction upon heating the crucible containing the tracer in 97% Ar, 3% O2 is disproportionation upon vaporization followed by oxidation and aggregation (14).

\[
\text{NaTcO}_4(s) \rightarrow \text{Tc}_2\text{O}_7(g) \quad \text{Eq. 1}
\]

\[
\begin{align*}
\text{Na} &\rightarrow \text{Na}^+ \\
\text{O} &\rightarrow \text{O}^-
\end{align*}
\]

Hydroscopic ditechnetium heptoxide can then undergo rapid hydrolysis with residual water in either the microaerosol generator or respiratory tract/transfer lines to form \(\text{Tc}_2\text{O}_7(\text{OH})^+\) and \(\text{TCO}_2(\text{OH})_2\).

\[
\text{Tc}_2\text{O}_7 \rightarrow \text{Tc}_2\text{O}_7(\text{OH}) \rightarrow \text{TcO}_2(\text{OH})_2 \quad \text{Eq. 2}
\]

The XPS results of thin films of condensed pertechnegas show convincing evidence for the existence of vaporized Tc-containing species with binding energy shifts for technetium in oxidation state +7, comparable to pertechnetate or hydrolyzed pertechnetate species. This was also confirmed in the chromatographic analysis. Our initial work with pertechnegas (1) also indicated that the biodistribution of the agent was identical with Na99mTcO4, progressively localizing in the thyroid, salivary glands, stomach, colon, kidneys and urinary bladder, after diffusion from the lungs. The rate of diffusion from the lungs was also identical with that of vaporized 99mTc pertechnetate. Subsequent to this, Bellen et al. (15) have demonstrated that the biological behavior of the agent was identical to 99mTc-pertechnetate in an animal model.

Therefore, pertechnegas may be viewed as possessing dual qualities. Depending on the viewpoint, it may be advantageous or not. Rapid clearance from the lungs and excretion by the kidneys reduces the radiation exposure to the lungs, but increases the dose to the kidneys, urinary bladder, thyroid and gastric mucosa. On the other hand, the dose of 99mTc macro-aggregated albumin can be significantly reduced and the count differential rate of perfusion to ventilation still maintained at 4 or 5 to 1, in order to obtain valid perfusion images.

Several patients with pulmonary emboli were found in this study. While none of these were confirmed by pulmonary angiography, they fulfilled the PIOPED criteria for a high probability scan and had both a high pre- and post-test probability of embolic disease. The segmental perfusion defects were normally ventilated in all five patients. None of these patients demonstrated prolonged retention of pertechnegas activity at the corresponding ventilatory site. Such a phenomenon has been described in an animal model of pulmonary arterial occlusion (16). The difference may be due to the more complex hemodynamic changes that follow lodgement of an embolus in the human lung, compared with occlusion of a branch of the pulmonary artery in the animal model.

CONCLUSION

Pertechnegas appears to possess the same physical characteristics, particle size range and ease of ventilation when compared to technegas. It allows high quality ventilatory images in spite of the rapid rate of clearance from the lungs. This phenomenon necessitates careful attention to the order in which images are acquired. The experience in this group of patients provided images of good quality that allowed classification of patients into the disease risk groups in the same manner as technegas. Limited comparison between technegas and pertechnegas demonstrated no significant difference in the information content of the images, although there was some degradation in the quality of the final image with pertechnegas. Mass spectrometric analysis of the agent reveals that a variety of molecular pertechnetate species including \(99\text{TcO}_2(\text{OH})_3\), \(99\text{TcO}_2(\text{OH})\) and \(99\text{NaTcO}_2(\text{OH})_2\) are generated when \(\text{Na}^{99\text{m}}\text{TcO}_4\) is resistively heated to 2500°C in a 3% O2/97% Ar mixture. These Tc species exist in oxidation +7, as confirmed by x-ray photoelectron studies.

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