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Evaluation of lung clearance of inhaled pertechnegas

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Pertechnegas is a new ventilation agent produced by modifying the atmosphere of combustion of Technegas. Due to its rapid disappearance from the lungs, Pertechnegas has been suggested as useful in measuring pulmonary epithelial permeability. This study aimed to assess the reliability of ventilation scans with Pertechnegas to evaluate alveolar-capillary permeability. Six non-smokers with no evidence of pulmonary disease were investigated. Scintigraphic data were used to evaluate the site of Pertechnegas deposition (by assessing the Penetration Index [PI] of the gas), its clearance rate (by calculating the time to half-clearance [$T_{1/2}$]) and its lung distribution (by means of a pixel-by-pixel analysis). PI measurements produced a mean value of 88.8 ± 13.3% (range 69–117%). Time activity curves showed a fast clearance in all cases (mean $T_{1/2}$ = 10.7 ± 2.1 min, range 8.1–14.3 min). Comparison of statistical indices of uniform deposition (skewness and kurtosis) indicated satisfactory homogeneity of Pertechnegas distribution throughout the lungs. These data show that after inhalation Pertechnegas has a peripheral deposition and a homogeneous distribution in the lungs and is rapidly cleared through the alveolar-capillary barrier. In conclusion Pertechnegas can be recommended as a potential radiopharmaceutical for studying the pulmonary epithelial barrier.

Key words: technetium 99m-diagnostic use; pulmonary epithelial permeability; technegas

INTRODUCTION

IN RECENT YEARS a new Technetium-agent for ventilation study has been introduced by Burch and colleagues. This radiopharmaceutical, Technegas, is obtained by heating sodium pertechnetate in a graphite crucible at 2500°C in an atmosphere of pure Argon.[1] The result is an ultra fine, dry aerosol which, once inhaled, exhibits peripheral penetration and prolonged pulmonary retention.[2] For these characteristics Technegas has rapidly become a widely used ventilation agent.[3,4] It has been demonstrated, however, that by appropriately modifying the atmosphere of combustion, a radiopharmaceutical with different properties can be produced.[5,6] This new agent, Pertechnegas, demonstrated pulmonary distribution similar to Technegas, but showed rapid disappearance from the lungs. Pertechnegas has therefore a fast lung clearance and it has been suggested that it is useful for measuring pulmonary epithelial permeability. Our study sought to assess the reliability of ventilation scans with Pertechnegas to evaluate alveolar-capillary permeability.

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MATERIALS AND METHODS

Pertechnegas production

Pertechnegas was obtained by a procedure similar to that used for preparing standard Technegas, except for the atmosphere filling the combustion chamber. 370–550 MBq of pertechnetate was placed in a graphite crucible in the Technegas Generator (Tetley Manufacturing Ltd., Sydney, Australia). A gas mixing system built "in-house" supplied the lead-lined chamber with an atmosphere of 96% argon and 4% oxygen. An electrical discharge then passed between two electrodes in the crucible, heating the graphite to 2500°C. The burn produced a fine, dry, radioactive aerosol that can be used for up to 10 minutes.

Patient population and pertechnegas delivery

Six volunteers without evidence of pulmonary disease were investigated; all the subjects were non-smokers. Pertechnegas was administered with the patient sitting in front of a gamma camera. The subjects were instructed to inhale slowly and hold their breath for about 3 seconds at maximum inspiration and then exhale back through the mouthpiece, using a nose clip to prevent nose breathing.[7] The breathing sequence was repeated till the desired count rate was reached (2000 cps). On the basis of previously observed rates per MBq, this target count rate corresponded to a retained activity of about 30 MBq of Pertechnegas.

Scintigraphic study

Images were dynamically recorded for 30 minutes (10 sec/frame) in posterior view into a 64 × 64 matrix, with a LFOV gamma camera (Apex 415, Elscint, Haifa, Israel) equipped with a LEGP collimator and interfaced to a computer (Apex SP1). Data acquisition started a few seconds before Pertechnegas breathing. To assess the site of Pertechnegas deposition the pulmonary Penetration Index (PI) of the gas was evaluated. Regions of Interest (ROI) were drawn around the central and peripheral zones of each lung. Pulmonary ROIs were determined for each lung by a threshold method applied within a loose ROI manually positioned in order to contain the whole lung. A central ROI was then obtained on the basis of an automatic method parametrized to the boundary of the lung master ROI.[8] In line with Agnew and coll.[9] PI was defined as the ratio of average peripheral counts to average central counts. Time activity curves were obtained for each lung and time to peak activity (T_{peak}) identified. A least squares single exponential fit was applied to the initial 7-minute data from T_{peak}, and time to half clearance ($T_{1/2}$) calculated for this phase.

Pertechnegas distribution determination

Pertechnegas distribution in both lungs was quantified by means of an automated pixel-by-pixel analysis of scan data. First, spatial 9-points weighted smoothing was applied to the whole study, then study images were grouped in 16 frames and images normalized to maximum count in the study and to the ROI area, and finally time-activity curves were generated from ROI data and 3-point weighted temporal smoothing applied. We therefore obtained images where the mean counts per lung pixel were independent of planar lung size and the Pertechnegas dose inhaled. For each normalized image a frequency distribution histogram was then constructed, plotting the count values on the *x*-axis and the number of pixels with a given count value on the *y*-axis. These histograms were analyzed in order to calculate the four moments of distribution (mean, standard deviation, skewness and kurtosis) by using the standard equations.[10,11]

Table 1 Penetration Index for each lung

Patient No.	PI left lung (%)	PI right lung (%)
1	76	69
2	80	89
3	85	89
4	86	78
5	102	117
6	93	102

Table 2 Time to half-clearance for each lung

Patient No.	$T_{1/2}$ left lung (minutes)	$T_{1/2}$ right lung (minutes)
1	11.8	13.2
2	8.9	8.1
3	8.7	10.2
4	13.2	14.3
5	10.1	8.6
6	11.6	9.7

RESULTS

In all cases administration of the gas was relatively easy; none of the patients complained of breathing difficulties and no side effects were recorded. Both lungs were clearly visualized after the first breath and the target count rate of 2000 cps was achieved in 3–7 breaths. Sequential images showed a relatively rapid disappearance of the gas from the lungs (Fig. 1).

PI measurements produced a mean value of 88.8% ± 13.3 (range 69%–117%); PI values are shown in Table 1.

Time activity curves showed in all cases a fast clearance (Fig. 2). $T_{1/2}$ values obtained for each lung are shown in Table 2. Mean $T_{1/2}$ was 10.7 ± 2.1 min (range 8.1–14.3 min).

As regards Pertechnegas distribution, normalized mean counts per pixel ranged from 18.30 to 24.40 with a mean ± s.d. of 21.46 ± 3.03. The standard deviation of counts per pixel ranged from 7.22 to 12.18 with a mean ± s.d. of 9.59 ± 2.12. Figure 3 shows a frequency distribution histogram (count values on the *x* axis and percentage of pixels with a given count value on the *y* axis).

To semiquantitatively evaluate the Pertechnegas distribution in the subjects lungs, we compared the two statistical indices of nonhomogeneous distribution: skewness (a measure of the histogram asymmetry) and kurtosis (a measure of the histogram range). The results are shown in Table 3 together with coefficients of variation (CV), calculated by dividing the standard deviation for counts per pixel by the mean count. The mean values for skewness, kurtosis and CV were 0.165 ± 0.068 (range 0.098–0.256), 2.205 ± 0.161 (range 2.049–2.388) and 0.44 ± 0.02 (range 0.42–0.47), respectively.

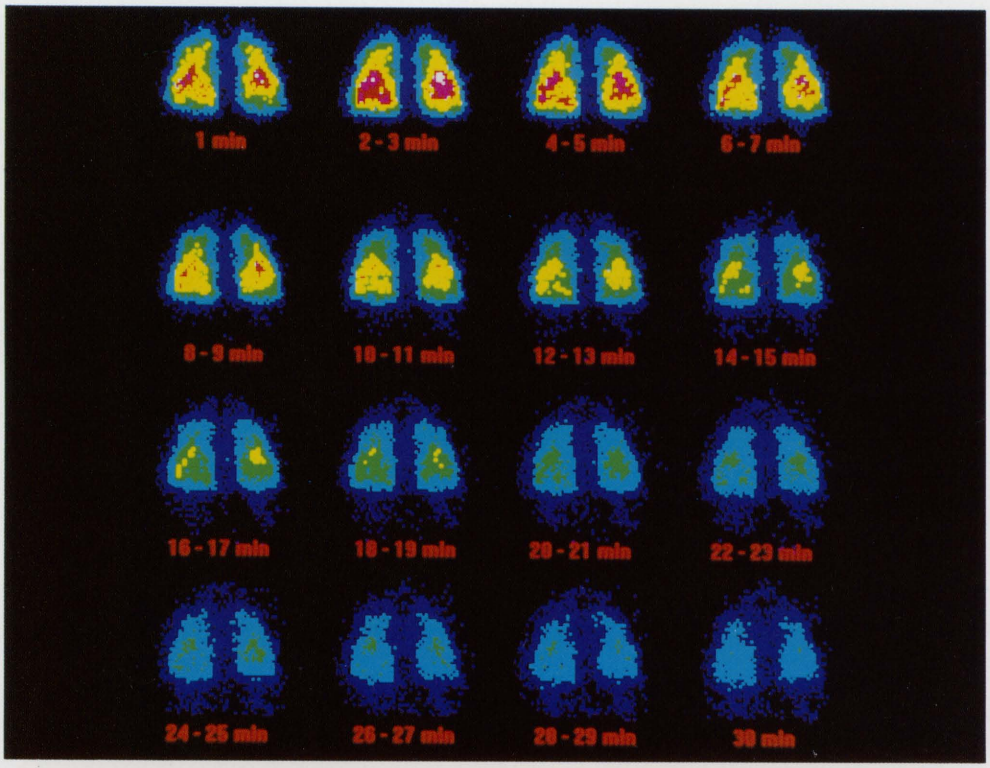

Fig. 1 Sequence of 2-min images showing a fast disappearance of Pertechnegas in both lungs.

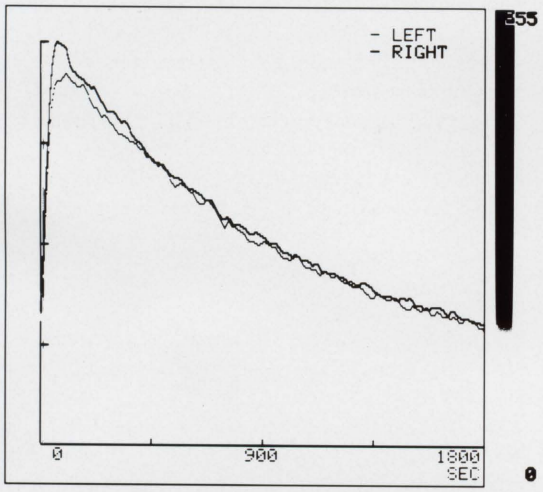

Fig. 2 Time-activity curves of patient no. 4. Left $T_{1/2}$ = 13.2 min. Right $T_{1/2}$ = 14.3 min.

Table 3 Mean skewness, kurtosis and coefficients of variation for the six patients

Patient No.	Skewness	Kurtosis	CV
1	0.108	2.078	0.45
2	0.220	2.289	0.44
3	0.110	2.057	0.47
4	0.098	2.049	0.45
5	0.200	2.388	0.42
6	0.256	2.368	0.44

DISCUSSION

Two key characteristics of Technegas are the small size of the inhaled particles[12] and the absence of significant clearance from the lungs.[13] These features enable ventilation studies to be performed with good peripheral penetration and prolonged pulmonary retention of the inhaled radiopharmaceutical.[3,13] It has, however, been observed that particle clearance rates are noticeably increased in the case of Pertechnegas, a different form of Technegas obtained by modifying the gas production procedure.[5,6] It has recently been demonstrated that the particle sizes of Technegas and Pertechnegas are similar,[14] both having a median diameter of about 160 nm and a geometric standard deviation of 1.6.[14] Pertechnegas shows signs of peripheral deposition and rapid clearance from the lung and it has been suggested that it is a potential tracer for evaluating pulmonary epithelial permeability.[5] In our study Pertechnegas was rapidly cleared with a $T_{1/2}$ of about 10 min, a value similar to those already reported.[12] Fast Pertechnegas clearance could be related to the small size of the gas molecules, given that it has been demonstrated that there is a relationship between the molecular weights of the inhaled agents and their rate of diffusion through a thin segment of the alveolar-capillary barrier.[15,16] Indeed the clearance rate of Pertechnegas is of the same order as that of aerosolized pertechnetate, therefore suggesting that Pertechnegas may be essentially vaporized

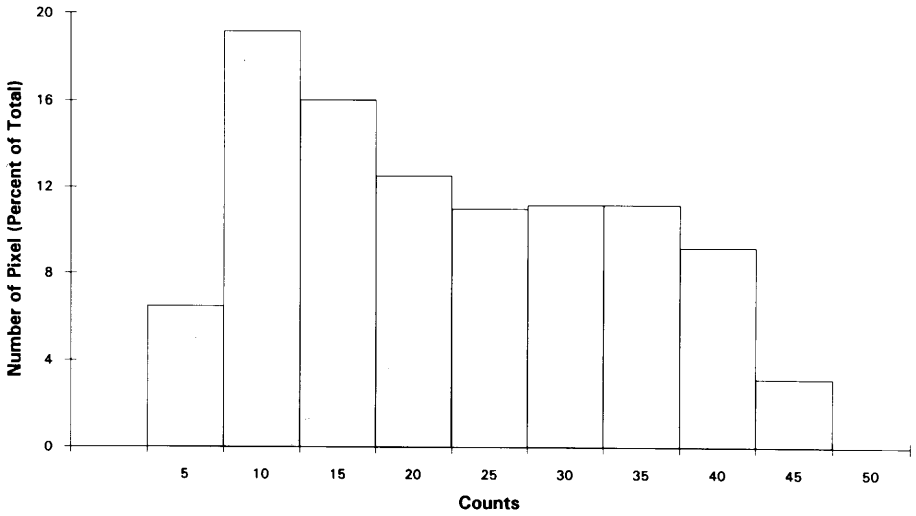

Fig. 3 Frequency distribution histograms for patient no. 4 (right lung).

pertechnetate.[17] It is not yet clear, however, how the modification of the combustion atmosphere determines a substantial change in gas characteristics in Technegas production.

Regarding the site of deposition, in our study Pertechnegas showed good peripheral deposition, similar to that reported for Technegas.[18] This feature of Pertechnegas may be very important when evaluating patients with impaired respiratory function. In fact Technegas showed greater peripheral penetration than other aerosols and reduced central deposition even in patients with chronic airways disease.[19,20] With respect to ^{99m}Tc-DTPA, currently used to evaluate pulmonary epithelial permeability, the site of deposition of Pertechnegas is probably less dependent on the inhalation technique,[21,22] and the tolerance of inhalation by dyspnoic patients is increased by the short duration of the procedure (2–5 breaths), which can also be performed with a ventilation assistance unit. Pertechnegas can therefore be particularly useful for evaluating the pulmonary epithelial permeability of patients with severe dyspnoea or even intubated on positive end expiratory pressure (PEEP) ventilation.

As for the uniformity of distribution, skewness and kurtosis seem to be good indices of distribution homogeneity. They are dimensionless, independent of lung size, and the total amount of deposited aerosol, and easy to calculate. It is important to define the lung boundary, but after that, the analysis of the deposition distribution histograms by skewness and kurtosis should be simple and useful. The low values obtained for skewness and kurtosis indicate homogeneous Pertechnegas distribution throughout the lungs. Obviously these consideration are limited by the fact that in our study scintigraphic data were acquired as planar images, thus including a volume factor: for a complete evaluation of gas distribution a dynamic tomographic study should have been performed. In conclusion, our data show that Pertechnegas distribution is peripheral and homogeneous, like that of Technegas. However Pertechnegas is proved to be rapidly cleared from the lungs, thus indicating that this approach may play a role in studying pulmonary epithelial permeability.

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