Utility of Technetium-99m-DTPA in Determining Regional Ventilation

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The goal of this study was to determine the usefulness of radiolabeled aerosols in the assessment of regional ventilation in tracheotomized patients maintained on mechanical ventilation. **Methods:** Three commercially available radioaerosol nebulizer kits were studied on the bench to determine nebulizer efficiency and particle distribution of ^{99m}Tc-DTPA aerosols. We studied ventilated tracheotomized human subjects with a gamma camera and simultaneously measured regional ventilation with ^{81m}Kr gas and ^{99m}Tc-DTPA aerosol. Images were compared by analysis of radioactivity distributions in computer-generated regions of interest. **Results:** The UltraVent nebulizing system produced the smallest particles with a mass median aerodynamic diameter of 0.9 μm compared to the AeroTech I and Venti-Scan II systems, which both produced aerosols of 1.3 μm. Despite relatively small particle sizes, ^{99m}Tc-DTPA deposition images with the UltraVent nebulizer did not accurately represent regional ventilation as measured by ^{81m}Kr equilibrium. Visual inspection of images revealed significant amounts of particle deposition in the region of the trachea which was diminished but not eliminated following replacement of the tracheotomy tube inner cannula. Based on regional analysis, correlation between radioactivity distributions of both isotopes was poor ($r = 0.262$, $p = 0.162$) with segmental analysis suggesting that the upper and middle lung regions were significantly affected by residual tracheal activity. **Conclusion:** The lungs of patients maintained on mechanical ventilation can be imaged after the inhalation of ^{99m}Tc-DTPA from commercially available delivery kits, but the correlation between aerosol deposition and regional ventilation is poor. Better definition of ventilated lung segments is obtained when using a gas such as ^{81m}Kr because tracheal activity with the radiolabeled gas is minimized.

Key Words: radiolabeled aerosols; krypton-81m; particle deposition; technetium-99m-DTPA

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The most common clinical indication for pulmonary scintigraphy is the evaluation of patients suspected of having pulmonary embolism (*1*). Perfusion lung imaging is highly sensitive but not specific in making the diagnosis (*2,3*). Its specificity, however, is enhanced when combined with ventilation measurements (*3,4*). Theoretically, ventilation is best measured using radioactive gases such as ^{133}Xe or ^{81m}Kr, but they have significant practical disadvantages (*5*). In the last decade, it has been recognized that the deposition of radiolabeled aerosols in the lungs can be used as an index of regional ventilation and, in spontaneously breathing patients, nebulized ^{99m}Tc-diethylenetriamine penta-acetate (DTPA) aerosols have been useful in diagnosing embolism (*6*).

Patients supported by mechanical ventilation can have all of the usual risk factors for embolic disease plus the added technical complication of the ventilator-airway apparatus. Butler et al. (*7*) and Vezina et al. (*8*) showed how deposition images could be obtained in ventilator-dependent patients, but they did not measure ventilation with a radioactive gas.

The purpose of this study was to practically assess ^{99m}Tc-DTPA aerosol as a tool to define ventilated lung regions in patients maintained on mechanical ventilation. As a prelude to clinical studies, we studied commercially available nebulizing systems on the bench to measure their efficiency and particle distribution of the generated aerosol. Then, utilizing techniques developed in spontaneously breathing and mechanically ventilated patients, we simultaneously measured regional ventilation with ^{99m}Tc-DTPA aerosol and ^{81m}Kr gas in five patients.

MATERIALS AND METHODS

In Vitro Bench Testing

In previous studies, we reported that mass-produced disposable plastic nebulizers, generally marketed for single use, do not exhibit uniform behavior between units from the same lot (*9*). Furthermore, it is not certain how many times a single unit can be serially studied without failure. Therefore, before performing bench studies of nebulizer output, particle size measurements and patient deposition, we pretested all nebulizers. After pretesting, each accepted device was only used once.

Nebulizer Pretesting

Three commercially available radioaerosol delivery systems (AeroTech I, CIS-US, Inc., Bedford, MA; Biodex Venti-Scan II, Shirley, NY; and Mallinckrodt UltraVent, St. Louis, MO) used by our hospital's nuclear medicine section were evaluated. Six units of each type were tested with a bench method previously described by McPeck et al. (*10*) to determine comparability. To standardize the volume fill of each nebulizer, every DTPA kit (Squibb, New Brunswick, NJ) was reconstituted with 150 mCi ^{99m}Tc in 2 ml saline. Then 15 mCi ^{99m}Tc-DTPA were withdrawn from the kit and reconstituted to 3 ml saline and placed in the nebulizer to be tested. The nebulizer was connected to a flow meter and operated at a flow rate of 10 liter/min until nebulization ceased. The outlet of each nebulizer was connected to a low-resistance absolute filter upon which the radioaerosol was collected (Fig. 1). After nebulization was complete, the filter medium was removed from its housing and placed in a radioisotope calibrator (Capintec CRC-10R, Montvale, NJ) to determine its radioactivity. After correction for decay, the radioactivity deposited on the filter was expressed as a percentage of the initial nebulizer activity.

After these tests, the mean and s.d. for each group was determined. Any nebulizer whose function lay outside of two s.d. of the mean was not used. The remaining nebulizers of each brand were set aside for approximately 24 hr to allow the radioisotope to decay and then rinsed with distilled water and flushed with dry air. Thereafter, by random selection, two of each brand were assigned to output studies, two were assigned to particle distribution measurements and any remaining units were not used. Based upon these results, a specific brand of nebulizer was selected and a second set of nebulizers was similarly pretested for the patient deposition studies.

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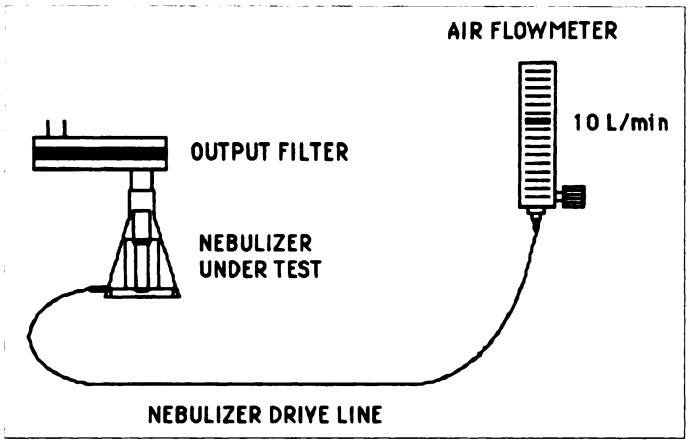

FIGURE 1. Preliminary testing of nebulizer function. Each nebulizer under testing was powered with air from a 50-psig backpressure compensated flow meter at 10 liters/min, and the output of radioactivity was collected on an absolute filter.

Technetium-99m-DTPA Aerosol Output

Output studies simulating standardized ventilator-patient conditions were conducted in vitro using a Puritan-Bennett (Carlsbad, CA) model 7200ae ventilator that had previously been characterized in this laboratory with respect to its nebulizer drive function (*10*). The ventilator with the nebulizer system under investigation was connected to a Bio-Tek (Winooski, VT) VT-1 single compartment test lung with compliance set at 0.025 l/cm H^2 and resistance set at 5 cm H_2O/liter/sec (Fig. 2). These test lung settings were maintained for all experiments. The ventilator was set in the control mode at breathing rate = 15/min, tidal volume = 1000 ml, square wave inspiratory flow pattern and inspiratory flow rate = 45 liter/min in order to yield a 1:2 I:E ratio with a 33% inspiratory time fraction (duty cycle). The FIO2 of each ventilator was set at 0.21 for all experiments. Because the presence of a heated, molecular-type of humidifier has been previously shown to diminish aerosol delivery to the output filter by a mean (±s.d.) of 41% ± 3.5% (*11*), we bypassed the humidifier during both the bench and the subsequent clinical studies.

None of the package inserts provided with the nebulizers contained instructions concerning the use of the system with a ventilator, but, upon inspection of each device, the method of connection to the ventilator circuit appeared obvious. The systems were attached to the Y-piece of the circuit in such a way as to utilize the integral filter to isolate the nebulizer and valve system from the ventilator circuit (Fig. 2). For each test run, a randomly chosen nebulizer from the group previously tested for comparability was filled with 2 ml ^{99m}Tc-DTPA in saline (nebulizer charge). The entire nebulizer was then placed in the radioisotope calibrator to measure its radioactivity. Aerosol delivery to the test lung (inhaled mass) was captured on the inhaled mass filter placed at the distal end of a Shiley (Irvine, CA) #8 disposable tracheotomy tube inner cannula (*11*). Filters were changed at 5-min intervals and the filter medium was removed from its housing and placed in the radioisotope calibrator to determine its radioactivity. This sequence was repeated until no further radioactivity was measured on the inhaled mass filter. In this manner, measurements on serial filters defined nebulizer function over time. Radioactivity at each interval was corrected for decay and expressed as a percentage of the initial nebulizer charge (inhaled mass %, the percentage of the nebulizer charge delivered to the filter). This quantity of radioactivity represents the mass of a tracer placed in the nebulizer that would have been inhaled by the patient (*11*) and represents the output of the nebulizer at that point in time.

Measurement of Particle Distribution

Two additional nebulizers from the group previously tested for comparability were charged with 2 ml ^{99m}Tc DTPA in saline (approximately 15 mCi). The test bench setup incorporating the ventilator, the nebulizer system, the #8 inner cannula and the test lung were all the same. A T-piece, however, was inserted into the circuit immediately proximal to the #8 inner cannula and its free limb was connected to a 10-stage cascade impactor (California Measurements, GS-1, Sierra Madre, CA) sampling at a rate of 1.0 liter/min for 2 min. The ventilator powered the nebulizer only during its inspiratory cycle. The particle distribution was determined by measuring the cumulative radioactivity on successive cascade impactor stages and plotting the values on probability paper. The resulting data were approximated by a straight line representing a log-normal distribution. The mass median aerodynamic diameter (MMAD) was read from the ordinate at the point where the straight line intersected the 50% value on the abcissa.

In Vivo Patient Studies

Five ventilator-dependent patients were recruited from our long-term ventilator care unit. They were free of signs of acute disease, e.g., bronchospasm and acute tracheobronchitis. Each patient's airway was maintained by tracheotomy and they were

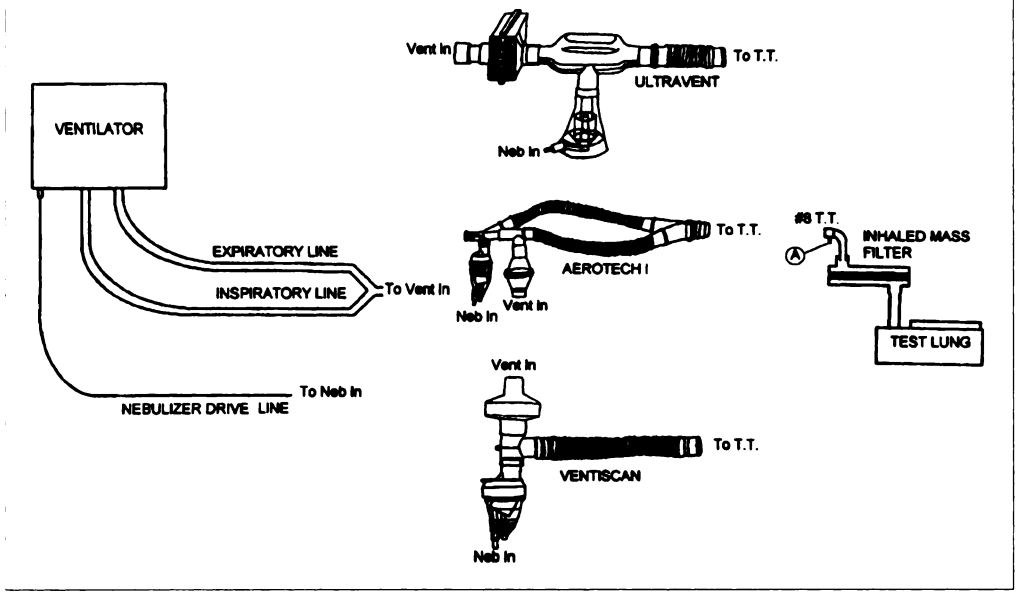

FIGURE 2. Schematic of the test bench setup for three brands of radioaerosol nebulizer systems (not to scale): Mallinckrodt UltraVent (top), CIS AeroTech I (middle), and Biodex Venti-Scan II (bottom). To measure aerosol delivery (inhaled mass %), the ventilator was connected to the high-efficiency particulate air (HEPA) filter (Vent In) that represents the inlet of each nebulizer system. The HEPA filter traps radioaerosol and prevents it from contaminating the ventilator and ambient environment. The patient connector of each nebulizer system was connected to a #8 tracheotomy tube (TT) inner cannula. A low-resistance absolute filter (inhaled mass filter) was interposed between the distal end of the TT and the mechanical test lung. The nebulizer drive line from the ventilator was connected to the Neb In fitting on each nebulizer. Sampling of the aerosol for particle size studies by cascade impactor was conducted through a connector located at point A.

TABLE 1
Patient Characteristics and Ventilator Settings

Patient no.	Age	Sex	Etiology of respiratory failure	LOSv (days)	Breathing rate* (breaths/min)	Tidal volume* (ml)
1	19	M	Quadriplegia	712	10	660
2	70	M	CVA, s/p CABG	2014	22	900
3	75	F	CVA, s/p laparotomy	138	17	700
4	74	M	s/p CABG, paralysis of L hemidiaphragm	176	20	850
5	69	M	MVA, CVA	33	18	740

*Breathing rate and tidal volume are the principle ventilator settings.
LOSv = length of stay on ventilator as of the day of testing. CVA = cerebral vascular accident; CABG = coronary artery bypass graft; MVA = motor vehicle accident.

mechanically ventilated with either a Bear 2 or Bear 3 ventilator (Bear Medical, Riverside, CA) in the assist/control or SIMV mode without PEEP. Informed consent was obtained and the protocol was approved by the Human Studies Committee of University Hospital. Each patient was studied on the ventilator that he/she had been using and at the ventilator settings that were in effect at the time of the study. Their clinical data and ventilator settings are listed in Table 1. An UltraVent nebulizer, selected randomly from a second set of nebulizers that had been bench tested to assure comparability, was connected to the ventilator circuit as shown in Figure 2. All studies were conducted in the patient's room using a portable gamma camera (GE Starcam, Milwaukee, WI) and the portable lead shielding supplied by the manufacturer for the nebulizer.

For the aerosol ventilation studies, the nebulizer was charged with 30 mCi ^{99m}Tc-DTPA to a volume of 2 ml. The same protocol utilized for the in vitro studies described previously was followed; namely, the humidifier was bypassed and the nebulizer was powered only during inspiration by the nebulizer driving system of the ventilator. At the start of nebulization, ^{81m}Kr was simultaneously introduced into the inspiratory line of the ventilator circuit. The patient's pulmonary radioactivity was monitored by the gamma camera (initially set for ^{81m}Kr). As activity in the lungs increased, the camera was positioned for an anterior image. After several minutes, ^{81m}Kr equilibrium was verified (less than 5% change in count rate over 15 sec serial test counts) and a krypton equilibrium scan was obtained and stored in the computer. Immediately after krypton imaging, the camera was switched to the ^{99m}Tc window and a count rate of approximately 100,000 cpm was verified (usually after 3–5 min of nebulization). The nebulizer was switched off and a ^{99m}Tc-DTPA deposition image obtained. Then, the inner cannula of the tracheotomy tube was changed (to reduce tracheotomy tube activity on the image) and a repeat deposition image acquired.

Image Analysis

The images were analyzed two ways: visual assessment in a manner similar to that used clinically (i.e., presence of a well-ventilated segment for ^{81m}Kr versus ^{99m}Tc-DTPA) and quantitative analysis. In previous studies, Köhn (*12*) demonstrated a good correlation between regional krypton and technetium activity in similarly performed experiments in spontaneously breathing patients. Using the ^{81m}Kr image as a template, a lung outline was drawn. Then, the lungs were divided into six regions as suggested by Köhn (*12*). The ^{81m}Kr regions were superimposed on the deposition images and regional radioactivity for each isotope was converted into a regional percentage by defining 100% as the total activity within the lung regions on a given image. Correlation between ^{81m}Kr and ^{99m}Tc activities were determined by linear regression.

TABLE 2
Pretesting of Nebulizers for Comparability Prior to Bench Testing and Clinical Studies

Nebulizer	Activity nebulized (% Charge)	Run time until dry (min)	Randomly selected disposition
UltraVent			
A1	43.8	12.5	Particle size study
A2	35.5	13.0	Outlier; not used
A3	46.1	13.0	Particle size study
A4	43.9	10.0	Inhaled mass study
A5	45.3	12.9	Not used
A6	42.0	16.3	Inhaled mass study
Mean (s.d.)	44.2 (1.4)	13.0 (2.0)	n = 5; outlier discarded
Venti-Scan II			
B1	46.0	6.0	Outlier; not used
B2	52.3	7.8	Particle size study
B3	51.1	7.7	Not used
B4	59.4	7.8	Particle size study
B5	57.1	8.8	Inhaled mass study
B6	56.8	8.0	Inhaled mass study
Mean (s.d.)	55.4 (3.1)	8.0 (0.4)	n = 5; outlier discarded
AeroTech I			
C1	50.4	6.0	Inhaled mass study
C2	48.4	7.7	Particle size study
C3	49.6	7.8	Inhaled mass study
C4	47.2	8.0	Not used
C5	37.9	9.5	Outlier; not used
C6	52.4	9.3	Particle size study
Mean (s.d.)	49.6 (1.8)	7.8 (1.1)	n = 5; outlier discarded
UltraVent			
D1	44.1	14.1	Patient 1
D2	39.5	14.6	Patient 2
D3	41.5	14.0	Patient 3
D4	41.8	12.7	Patient 4
D5	40.0	14.7	Patient 5
Mean (s.d.)	41.4 (1.8)	14.0 (0.8)	n = 5

RESULTS

Results of the preliminary nebulizer comparability experiments are listed in Table 2. After deletion of any outlier, the mean quantity of aerosol produced by the different nebulizers varied from 41.4% to 55.4% of the nebulizer charge. For each device, however, the variation between the remaining examples was relatively small (s.d. ± 1.4 to 3.1). Table 2 also lists the fate of each nebulizer in subsequent experiments (i.e., nebulizer output, particle distribution studies or not used). The first set of UltraVent nebulizers (A1 to A6) were used in preliminary bench testing only; the second set (D1 to D5) were used in the patient deposition studies.

Figure 3 shows the inhaled mass data for each of the three brands. While the different nebulizers seemed to function relatively similarly in pretesting (Table 2), the performance of the nebulizer/tubing/ventilator combinations was significantly more variable. Duplicate experiments revealed that the AeroTech I was nearly twice as efficient as the UltraVent and Venti-Scan II systems with between 30 and 35% of the original amount of ^{99m}Tc-DTPA placed in the nebulizer (nebulizer charge) reaching the filter at the distal tip of the tracheotomy

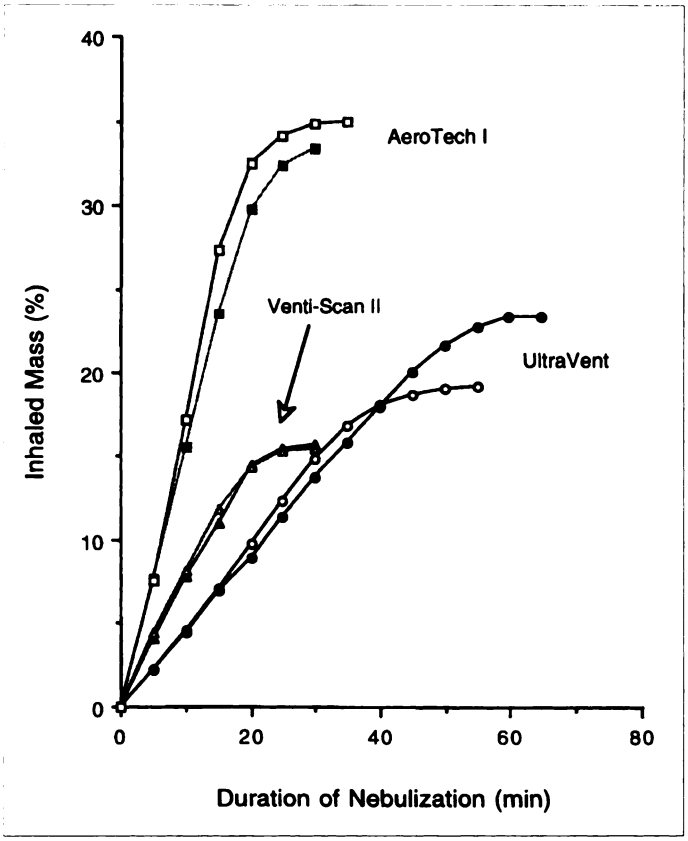

FIGURE 3. Percentage of inhaled mass (percentage of initial nebulizer charge) over time, measured at the distal end of a #8 tracheotomy tube inner cannula. Measurements of radioactivity were made at 5-min intervals until the nebulizer ran dry. Nebulization to dryness is indicated by the development of a plateau.

tube. Furthermore, the slope of the AeroTech I curve is about twice as steep as the other brands, indicating more rapid delivery of aerosol with a plateau in approximately 20 min.

The mass median aerodynamic diameters were similar for the AeroTech I and Venti-Scan II at 1.3 μm, σ = 1.92. The UltraVent produced the smallest particles at 0.9 μm, σ = 1.67.

Decision Regarding Choice of Delivery System

From the bench data, the AeroTech I was the most efficient delivery system. The UltraVent produced the smallest particles proximal to the tracheotomy tube. In spontaneously breathing patients, the major factor affecting interpretation of ^{99m}Tc-DTPA aerosol ventilation scans is the central deposition of particles (*6,17*). Therefore, the UltraVent system, with its smaller particles, was chosen for the patient studies in an attempt to minimize central deposition. To compensate for the relative inefficiency of that nebulizer, we used 30 mCi of ^{99m}Tc-DTPA as the nebulizer charge in the human studies. This allowed completion of the deposition/ventilation measurements in the shortest time possible (usually within 5 min) to reduce possible artifacts from ^{99m}Tc-DTPA clearance.

Human Ventilation Studies

Gamma camera images for the simultaneously performed ventilation and deposition studies are shown for the five patients in Figure 4. The regions of interest drawn over the ^{81m}Kr equilibrium image and superimposed on the ^{99m}Tc-DTPA scans are also shown. Pulmonary ventilation appears to be well defined for all patients with separation of ^{81m}Kr activity in the tubing from the lung images. Obvious nonuniformities were detected. For example, the entire right lung of Patient 1 was not ventilated. Inspection of the ^{99m}Tc-DTPA images reveals significant deposition in the tracheotomy area that, in general, is reduced but not eliminated upon removal of the tracheotomy tube's inner cannula. With the availability of the ^{81}Kr data, it is easier to assess the ^{99m}Tc-DTPA scans. Patient 1 does not ventilate the right lung and each region of the left lung is seen with both the radioactive gas and aerosol images. Similar concordance of ventilation and particle deposition is seen for Patient 2. On the other hand, the images for Patients 3, 4 and 5 do not reveal the lung periphery because of enhanced activity in the trachea as well as central deposition of particles. The effect of tracheal deposition on image assessment is further illustrated by the observation that the lung periphery is better seen in all patients when the tracheal activity is reduced by changing the inner cannula. This maneuver does not remove all of the tracheal activity. Some activity remains as a likely consequence of turbulent deposition in the trachea.

Image analysis was quantified by analyzing regional activity from the ^{81m}Kr images and the corresponding ^{99m}Tc-DTPA images acquired after the tracheotomy tube was changed to minimize the effect of tube deposition. On a percentage basis, the distribution of deposited ^{99m}Tc-DTPA does not correlate well with the equilibrium distribution of ^{81m}Kr. With each patient's lung divided into six regions, the overall correlation coefficient is only 0.262, $p = 0.162$. The influence of the tracheal deposition is apparent when the regional analysis is correlated for the upper, middle and lower lung zones separately. Under those conditions, the distribution of krypton and technetium in lung regions abutting the tracheotomy do not correlate significantly ($r = 0.274$, $p = 0.444$ and $r = 0.456$, $p = 0.186$ for the upper and middle zones, respectively), while there is a significant correlation in the lower lung regions between both isotopes ($r = 0.742$, $p = 0.0141$).

DISCUSSION

This study demonstrates that regional ventilation cannot be well approximated with ^{99m}Tc-DTPA aerosols in mechanically ventilated patients. Our findings differ from those reported by Butler et al. (*7*), whose group performed a retrospective study comparing ventilation/perfusion scans in mechanically ventilated as well as spontaneously breathing patients suspected of having pulmonary embolism. They concluded that ^{99m}Tc-DTPA aerosol scans in mechanically ventilated patients are associated with good peripheral penetration of activity. The frequency, however, of a reverse mismatch was significantly higher in the mechanically ventilated group.

Whereas there can be multiple causes for reverse mismatch, it can be expected if the measure of ventilation does not penetrate to the lung periphery. This was the case in our patients, as well as the case reported Butler et al. (*7*). Our study suggests that reverse mismatch can be reduced if ventilation is quantified with a gas (Fig. 4).

Our findings also differ from those reported by Köhn (*12*) who studied spontaneously breathing patients. Köhn performed a comparative analysis of krypton and aerosol deposition images in patients with varying degrees of obstructive disease. Using the same analytical approach (linear regression, six lung regions), he found a good correlation between ^{81m}Kr and ^{99m}Tc-DTPA ($r = 0.94$, $p < 0.001$). The particles used by Köhn were smaller than those of our study (0.37 μm versus 0.9 μm). Furthermore, in a more recent study, a similar correlation to that of Köhn was reported by O'Riordan and Smaldone (*13*) in spontaneously breathing patients using particle distributions that ranged as large as 2.5 μm. Therefore, the failure of our ^{99m}Tc-DTPA data to correlate with regional ventilation as assessed by ^{81m}Kr is likely related to deposition in the trache-

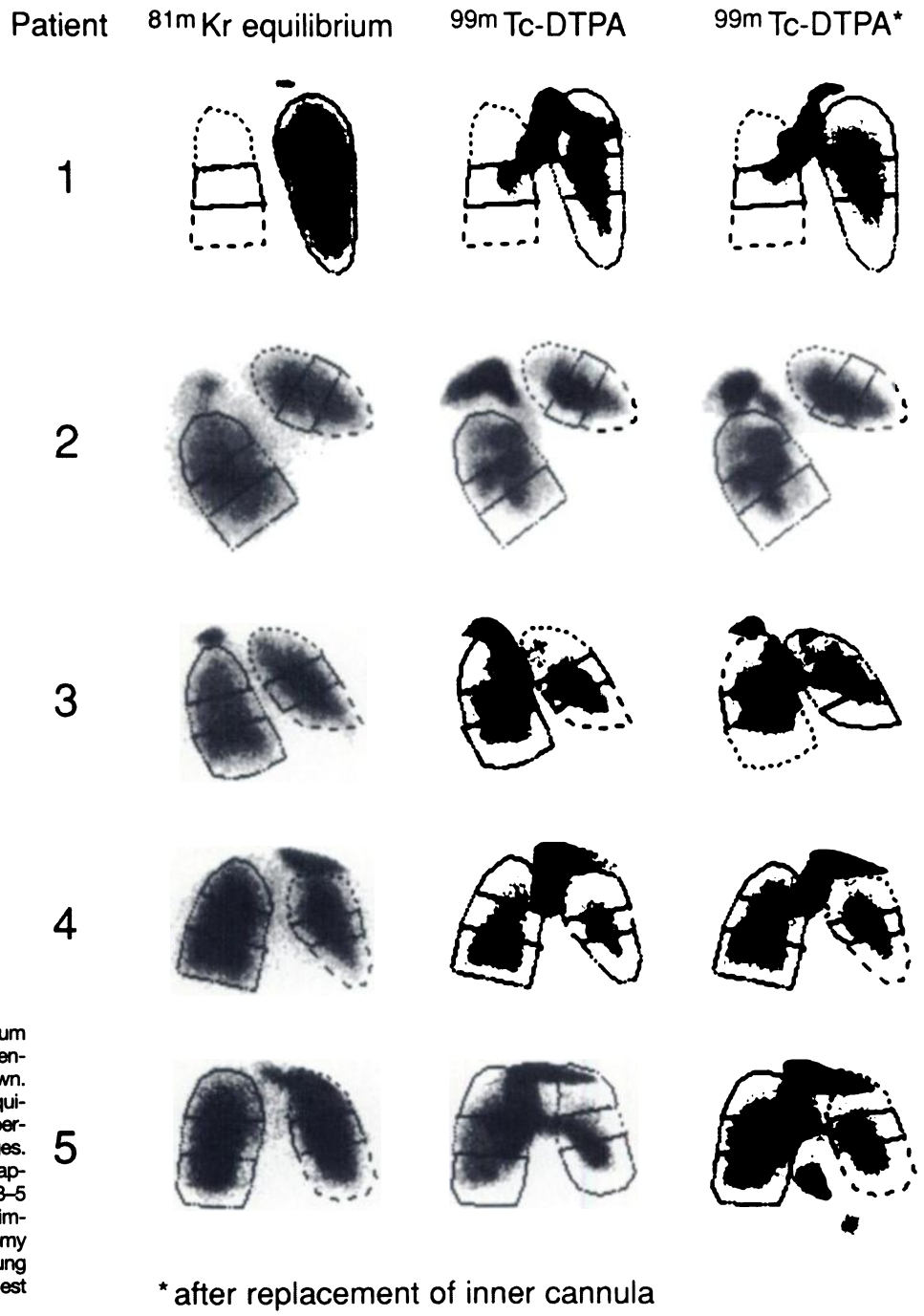

FIGURE 4. Krypton equilibrium and technetium deposition images obtained in five ventilator-dependent patients. Actual patient orientation is shown. The lung outline was determined by an ^{81m}Kr equilibrium image (left column) and subsequently superimposed over the ^{99m}Tc-DTPA deposition images. (Middle column) Deposition images obtained at approximately 100,000 cpm after approximately 3–5 min of nebulization. (Right column) Deposition images obtained immediately after the tracheotomy tube inner cannula was replaced. The right lung outline for Patient 1 was estimated from the chest radiograph.

otomy tube and trachea and not to particle size distribution per se and its effects on lung parenchymal deposition. This conclusion is supported by the improved relationship found for the lower lung regions which are not strongly affected by tracheal activity and the lack of significant upper airway deposition reported in spontaneously breathing patients inhaling similar aerosols (*13,14*).

The bench studies indicate that use of the other commercially available aerosol delivery systems that we studied will not improve the results because both the AeroTech I and Venti-Scan II produce larger particles; therefore, it is unlikely that tracheal deposition will be reduced. Furthermore, we do not expect significant differences in the pattern of deposition between patients intubated with endotracheal tubes and our tracheotomized patients. Other investigators have reported similar degrees of tracheal deposition in intubated patients following aerosol inhalation (*15*).

Different factors determine regional ventilation and regional particle deposition. Regional ventilation is dependent on local pulmonary compliance and airway resistance (*16*). The factors influencing particle deposition are more complex. Regional ventilation is required to deliver a particle but the tendency of a region to retain that particle is determined by three processes: gravitational sedimentation, inertial impaction, and to a lesser extent, diffusion. The relative importance of each process is in turn determined by the density, diameter and diffusion coefficient of the inhaled particle, its residence time in the airway, local airway anatomy and the rate of airflow (*17*). In a recent editorial, O'Riordan and Smaldone (*14*) assessed the predictive value of aerosol studies in measuring regional ventilation. They evaluated studies in normal subjects and patients with obstructive and restrictive lung disease and concluded that quantitative measurement of regional ventilation is best accomplished with radioactive gases rather than radiolabeled aerosols. They did,

however, show that the findings of Köhn (*12*) were consistent with the clinical studies of Alderson et al. (*2*), which indicated that aerosol studies were adequate to assess whether a lung segment is ventilated or not in the context of a diagnostic evaluation of pulmonary emboli. Aerosol studies, however, were not sufficiently accurate to quantitate local ventilation (e.g., prior to resectional surgery). Finally, our results indicate that, because of turbulent tracheal deposition, ^{99m}Tc-DTPA studies may be inadequate for the assessment of pulmonary emboli in mechanically ventilated patients.

CONCLUSION

The lungs of patients maintained on mechanical ventilation can be imaged after inhalation of ^{99m}Tc-DTPA from commercially available delivery kits, but the correlation between aerosol deposition and regional ventilation is poor. Better definition of ventilated lung segments is obtained when using a gas such as ^{81m}Kr.

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Phase 1 Study of Rhenium-186-HEDP in Patients with Bone Metastases Originating from Breast Cancer

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Rhenium-186-1,1-hydroxyethylidene diphosphonate (^{186}Re-HEDP) has been used for the palliative treatment of metastatic bone pain. A Phase 1 dosage escalation study was performed using ^{186}Re-HEDP in patients with metastatic breast cancer. **Methods:** Twelve patients with metastatic breast cancer were studied. Each patient had at least four bone metastases and adequate hematological function. Groups of three consecutive patients were treated with dosages starting at 1295 MBq (35 mCi) and increasing to 2960 MBq (80 mCi) (escalated in increments of 555 MBq). **Results:** A transient increase in pain ("flare" reaction) was observed in six patients. Two patients who received 2960 MBq ^{186}Re-HEDP showed Grades 3 (platelets 25–50 $\times$ 10^9/l) and 4 (platelets $< 25 \times 10^9$/l) platelet toxicity, which was defined as unacceptable. Prior to treatment, alkaline phosphatase levels were elevated in seven cases. These patients showed a transient decline in alkaline phosphatase levels during the first 4 wk. **Conclusion:** The maximum tolerated administered activity of ^{186}Re-HEDP in patients with metastatic breast cancer is 2405 MBq (65 mCi). Thrombocytopenia proved to be the dose-limiting toxicity, which could not be predicted adequately by the administered activity. Changes of alkaline phosphatase levels suggest anti-tumor effects of ^{186}Re-HEDP.

Key Words: breast cancer; bone metastases; rhenium-186-HEDP; dosage escalation; bone marrow toxicity

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Bone is the most common site of metastatic disease in breast cancer patients. The majority of patients with advanced breast cancer have evidence of bone metastases by time of death (*1*). The most prominent symptom associated with bone metastases is pain, which characteristically develops gradually over weeks or months and becomes progressively more severe (*2*).

Bone metastases require treatment in order to palliate pain. Localized external-beam radiotherapy is an effective modality in the treatment of bone pain and offers partial or complete relief in 73%–96% of patients treated (*3,4*). The probability of relief appears slightly better with bone metastases from breast cancer as compared with the instance of carcinoma of the kidney or prostate (*2*). A common problem in this group of

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